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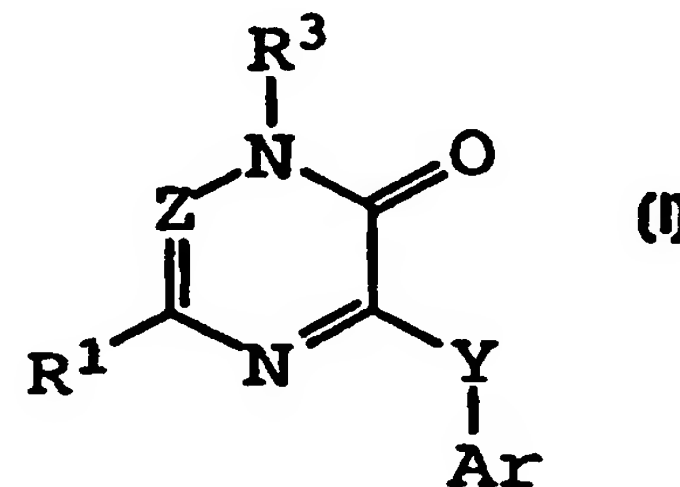
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(54) Title: PYRAZINONES AND TRIAZINONES AND THEIR DERIVATIVES THEREOF

(57) Abstract

Corticotropin releasing factor (CRF) antagonists of Formula (I), and their use in treating psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorders, supranuclear palsy and eating disorders.



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TITLE

PYRAZINONES AND TRIAZINONES AND THEIR DERIVATIVES THEREOF

FIELD OF THE INVENTION

5 This invention relates to novel compounds and pharmaceutical compositions, and to methods of using same in the treatment of psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorders, supranuclear palsy and eating disorders.

BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin(POMC)-derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Nat. Acad. Sci. (USA)* 80:4851 (1983); W. Vale et al., *Science* 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., *Rec. Prog. Horm. Res.* 39:245 (1983); G.F. Koob, *Persp. Behav. Med.* 2:39 (1985); E.B. De Souza et al., *J. Neurosci.* 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (1989); J.E. Morley, *Life Sci.* 41:527 (1987)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and eating disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's

disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (1988)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (1984); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (1987); R.D. France et al., *Biol. Psychiatry* 28:86 (1988); M. Arato et al., *Biol Psychiatry* 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (1984); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (1984); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)]. There is preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

There has also been a role postulated for CRF in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., *Life Sci.* 31:363 (1982); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (1986)]. Preliminary studies using the putative CRF receptor

- antagonist α -helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (1987), *Brain Research Reviews* 15:71 (1990)]. Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics providing further evidence for the involvement of CRF in these disorders.
- 10 Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., *Psychopharmacology* 86:170 (1985); K.T. Britton et al., *Psychopharmacology* 94:306 (1988)] and in the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 15 88:147 (1986)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the 20 actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (1988)].

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been 25 hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (α -helical CRF9-41) in a variety of behavioral 30 paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)]. 35

DuPont Merck PCT application WO95/10506 describes corticotropin releasing factor antagonist compounds

and their use to treat psychiatric disorders and neurological diseases.

European patent application 0 576 350 A1 by Elf Sanofi describes corticotropin releasing factor antagonist compounds useful in the treatment of CNS and stress disorders.

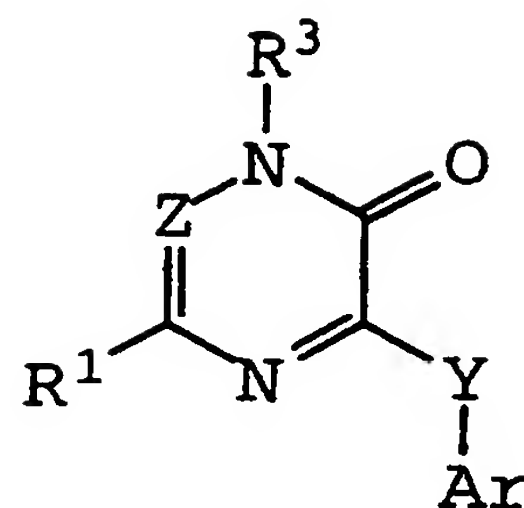
Pfizer patent applications WO 94/13676, WO 94/13677, WO 94/13661, WO 95/33750, WO 95/34563, WO 95/33727 describe corticotropin releasing factor antagonist compounds useful in the treatment of CNS and stress disorders.

All of the aforementioned references are hereby incorporated by reference.

The compounds and the methods of the present invention provide for the production of compounds capable of inhibiting the action of CRF at its receptor protein in the brain. These compounds would be useful in the treatment of a variety of neurodegenerative, neuropsychiatric and stress-related disorders such as affective disorders, anxiety, depression, post-traumatic stress disorders, supranuclear palsy, seizure disorders, stroke, irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other eating disorders, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorders and fertility problems. It is further asserted that this invention may provide compounds and pharmaceutical compositions suitable for use in such a method.

SUMMARY OF THE INVENTION

This invention is a class of novel compounds which are CRF receptor antagonists and which can be represented by Formula (I):



(I)

or a pharmaceutically acceptable salt form thereof, wherein
 5 Z is CR² or N;

when Z is CR²:

Y is NR⁴, O or S(O)_n;

Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl,
 10 pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, furanyl,
 quinolinyl, isoquinolinyl, thienyl, imidazolyl,
 thiazolyl, indolyl, indolinyl, pyrrolyl, oxazolyl,
 benzofuranyl, benzothienyl, 2,3-dihydrobenzofuranyl,
 2,3-dihydrobenzothienyl, benzothiazolyl, indazolyl,
 15 isoxazolyl or pyrazolyl, each substituted with 0 to 4
 R⁵ groups; wherein Ar is attached to Y through an
 unsaturated carbon;

R¹ is H, halo, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-
 C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl,
 20 heterocyclyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷,
 -CONR⁶R⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂,
 -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, or -NR⁶R⁷,
 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl
 or C₃-C₈ cycloalkyl is each substituted with 0 to 3
 25 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
 C₁-C₄ haloalkyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷,
 -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷,
 -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl;

30 R² is H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
 C₃-C₆ cycloalkyl, halo, -CN, C₁-C₄ haloalkyl, -NR⁹R¹⁰,
 -NR⁹COR¹⁰, -NR⁹CO₂R¹⁰, -OR¹¹, -SH or -S(O)_nR¹²;

- R^3 is C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -OR⁷, -S(O)₂R¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -CONR⁶R⁷, -NR⁸CO₂R⁷, or -NR⁶R⁷,
 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl, with the proviso that when R^3 is aryl, Ar is not imidazolyl;
- R^4 is H, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl, wherein C₂-C₆ alkenyl or C₂-C₆ alkynyl is optionally substituted with C₁-C₄ alkyl or C₃-C₆ cycloalkyl and wherein C₁-C₆ alkyl is optionally substituted with C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, -OR⁷, -S(O)_nR¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;
- R^5 is independently selected at each occurrence from C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, heterocyclyl, -NO₂, halo, -CN, C₁-C₄ haloalkyl, -NR⁶R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷, -OR⁷, -COR⁷, -CO₂R⁷, -CONR⁶R⁷, -CON(OR⁹)R⁷, -SH, and -S(O)_nR¹³, wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN, -OR⁷, -COR⁷, -CO₂R⁷, -CONR⁶R⁷, -NR⁶R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷ and -S(O)_nR¹³;
- R^6 and R^7 are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl, heterocyclyl(C₁-C₄ alkyl)-,

morpholinoethyl, morpholinopropyl and morpholinobutyl; or $-NR^6R^7$ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

5 wherein C₁-C₄ alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C₁-C₄ alkoxy groups;

R⁸ is independently at each occurrence H or C₁-C₄ alkyl;

R⁹ and R¹⁰ are independently at each occurrence selected

10 from H, C₁-C₄ alkyl and C₃-C₆ cycloalkyl;

R¹¹ is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;

R¹² is C₁-C₄ alkyl, C₁-C₄ haloalkyl or $-NR^6R^7$;

R¹³ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl,

15 C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, $-NR^6R^7$, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-;

R¹⁴ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, $-NR^{15}R^{16}$;

20 R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl; or $-NR^{15}R^{16}$ taken together as a whole is piperidine, pyrrolidine, piperazine,

25 N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl, biphenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR¹⁵, -SH, -S(O)_nR¹⁴, -COR¹⁵,

30 -CO₂R¹⁵, -OC(O)R¹⁴, -NO₂, -NR⁸COR¹⁵, -N(COR¹⁵)₂, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵, -NR¹⁵R¹⁶ and -CONR¹⁵R¹⁶;

heterocyclyl is 5- to 10- membered heterocyclic ring which may be saturated, partially unsaturated or aromatic, and which consists of carbon atoms and from 1 to 4

35 heteroatoms independently selected from the group consisting of N, O and S, wherein the heterocyclic ring is substituted with 0 to 3 substituents

independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR¹⁵, -SH, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -OC(O)R¹⁴, -NR⁸COR¹⁵, -N(COR¹⁵)₂, -NR⁸CONR¹⁵R¹⁶,
 5 -NR⁸CO₂R¹⁵, -NR¹⁵R¹⁶, and -CONR¹⁵R¹⁶; and
 n is independently at each occurrence 0, 1 or 2;

and wherein, when Z is N:

Y is NR⁴, O or S(O)_n;

10 Ar, R¹, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, aryl, heterocyclyl, heterocyclyl and n are as defined above, but

R³ is C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl,
 15 heterocyclyl, -CN, -S(O)₂R¹³, -CO₂R⁷, -COR⁷ or -CONR⁶R⁷,
 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each
 20 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl,
 with the proviso that when R³ is aryl, Ar is not
 25 imidazolyl.

[3] Preferred compounds of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

30 Z is CR²;
 Y is NR⁴ or O;
 Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵ groups;
 35 R¹ is H, halo, C₁-C₄ alkyl, cyclopropyl, C₁-C₄ haloalkyl, -CN, -NR⁶R⁷, -CONR⁶R⁷, -OR⁷, -COR⁷, -CO₂R⁷ or -S(O)_nR¹³,

- wherein C₁-C₄ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, C₃-C₆ cycloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷, -NR⁶R⁷ and aryl;
- R² is H, C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl;
- R³ is C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -OR⁷, -S(O)₂R¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -CONR⁶R⁷, -NR⁸CO₂R⁷, or -NR⁶R⁷, wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -CO₂R⁷, -NR⁸COR⁷, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, aryl and heterocyclyl;
- R⁴ is H, C₁-C₆ alkyl or C₂-C₆ alkenyl, wherein C₁-C₆ alkyl is optionally substituted with C₁-C₄ alkyl, C₁-C₄ haloalkyl, -OR⁷, -S(O)_nR¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;
- R⁵ is independently selected at each occurrence from C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₄-C₈ cycloalkylalkyl, aryl, heterocyclyl, C₁-C₄ haloalkyl, halo, -CN, -NO₂, -NR⁶R⁷, -COR⁷, -OR⁷, -CONR⁶R⁷, -CON(OR⁹)R⁷, CO₂R⁷ and -S(O)_nR¹³, wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl and C₄-C₈ cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN, -NR⁶R⁷, COR⁷, -OR⁷, -CONR⁶R⁷, CO₂R⁷ and -S(O)_nR¹³;
- R⁶ and R⁷ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-

- C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl, heterocyclyl(C₁-C₄ alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or -NR⁶R⁷ taken together as a whole
- 5 is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C₁-C₄ alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C₁-C₄ alkoxy groups;
- 10 R⁸ is independently at each occurrence H or C₁-C₄ alkyl; R⁹ and R¹⁰ are independently at each occurrence selected from H, C₁-C₄ alkyl and C₃-C₆ cycloalkyl; R¹¹ is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;
- 15 R¹² is C₁-C₄ alkyl, C₁-C₄ haloalkyl or -NR⁶R⁷; R¹³ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR⁶R⁷, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-;
- 20 R¹⁴ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR¹⁵R¹⁶; R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl and C₄-
- 25 C₁₂ cycloalkylalkyl; or -NR¹⁵R¹⁶ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine; aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from
- 30 C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵ and -NR¹⁵R¹⁶;
- heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3
- 35 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵,

$-S(O)_nR^{14}$, $-CO_2R^{15}$, $-NO_2$, $-NR^8COR^{15}$, $-NR^8CONR^{15}R^{16}$,
 $-NR^8CO_2R^{15}$, and $-NR^{15}R^{16}$; and

n is independently at each occurrence 0, 1 or 2.

5 [4] More preferred compounds of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

Z is CR^2 ;

10 Y is NR^4 ;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R^5 groups;

15 R^1 is H, halo, C_1 - C_4 alkyl, cyclopropyl, C_1 - C_3 haloalkyl, $-CN$, $-NR^6R^7$, $-CONR^6R^7$, $-COR^7$, $-CO_2R^7$, $-OR^7$ or $-S(O)_nR^{13}$ wherein C_1 - C_4 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_3 - C_4 cycloalkyl, halo, $-CN$, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^6R^7$;

R^2 is H;

20 R^3 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_1 - C_4 haloalkyl or aryl, wherein C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl or C_3 - C_6 cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_4 haloalkyl, halo, $-CN$, $-OR^7$, $-S(O)_nR^{13}$, $-CO_2R^7$, $-NR^8COR^7$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^7$, $-NR^6R^7$ and aryl;

25 R^4 is H, allyl, or C_1 - C_4 alkyl, wherein C_1 - C_4 alkyl is optionally substituted with C_1 - C_4 alkyl, $-OR^7$, $-S(O)_2R^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;

30 R^5 is independently selected at each occurrence from C_1 - C_6 alkyl, aryl, heterocyclyl, C_1 - C_4 haloalkyl, halo, $-CN$, $-NO_2$, $-NR^6R^7$, $-COR^7$, $-OR^7$, $-CONR^6R^7$, $-CON(OR^9)R^7$, $-CO_2R^7$ and $-S(O)_nR^{13}$, wherein C_1 - C_6 alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C_1 - C_4 alkyl, $-NO_2$,

35

halo, -CN, -NR⁶R⁷, COR⁷, -OR⁷, -CONR⁶R⁷, CO₂R⁷ and
-S(O)_nR¹³;

R⁶ and R⁷ are independently selected at each occurrence
from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₂-C₈
alkoxyalkyl;

wherein C₁-C₄ alkyl, may be substituted with 0 to 2
substituents independently selected at each
occurrence from -OH or C₁-C₄ alkoxy groups;

R⁸, R⁹ and R¹⁰ are independently at each occurrence H or
C₁-C₄ alkyl;

R¹² and R¹³ are independently at each occurrence C₁-C₄
alkyl or -NR⁶R⁷;

R¹⁴ is C₁-C₄ alkyl or -NR¹⁵R¹⁶;

R¹⁵ and R¹⁶ are independently at each occurrence H, C₁-C₄
alkyl or C₂-C₈ alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents
independently selected at each occurrence from
C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵,
-CO₂R¹⁵, -NO₂ and -NR¹⁵R¹⁶; and

n is independently at each occurrence 0, 1 or 2.

[5] Even more preferred compounds of this invention
are compounds of Formula (I) and pharmaceutically
acceptable salts and pro-drug forms thereof, wherein:

Z is CR²;

Y is NR⁴;

Ar is phenyl or pyridyl, each substituted with 2 to 4 R⁵
groups;

R¹ is H, Cl, Br, methyl, ethyl, cyclopropyl, or -CN,
R² is H;

R³ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,
C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl or aryl,
wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or
C₃-C₆ cycloalkyl is each substituted with 0 to 3
substituents independently selected at each

- occurrence from C₁-C₄ alkyl, C₃-C₆ cycloalkyl, -CF₃, halo, -CN, -OR⁷, and aryl;
- R⁴ is H, methyl, ethyl, i-propyl, n-propyl, n-butyl, i-butyl, s-butyl, n-butyl, or allyl;
- 5 R⁵ is independently selected at each occurrence from methyl, ethyl, i-propyl, n-propyl, aryl, -CF₃, halo, -CN, -N(CH₃)₂, -C(=O)CH₃, -OCH₃, -OCH₂CH₃, -OCF₃, and -S(O)₂CH₃;
- R¹⁴ is C₁-C₄ alkyl or -NR¹⁵R¹⁶;
- 10 R¹⁵ and R¹⁶ are independently at each occurrence H, C₁-C₄ alkyl or C₂-C₈ alkoxyalkyl;
- aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂ and -NR¹⁵R¹⁶; and
- 15 n is independently at each occurrence 0, 1 or 2.

[6] Specifically preferred compounds of this invention are compounds of Formula (I), pharmaceutically acceptable salts and pro-drug forms thereof, which are:

20

- 3-[(2,4-Dibromophenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;
- 3-[[2-Bromo-4-(1-methylethyl)phenyl]amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;
- 25 3-[(2,4-Dibromophenyl)ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;
- 3-[[2-Bromo-4-(1-methylethyl)phenyl]ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;
- 30 3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;
- 3-[(2,4,6-Trimethylphenyl)ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;
- (+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
- 35 3-[(2-Bromo-4,6-dimethoxyphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

- 3-[(2-Cyano-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
(+/-)-3-[(2-Bromo-4,6-dimethoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
5 (+/-)-3-[(2-Chloro-4,6-dimethoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
(+/-)-3-[(4,6-Dimethyl-2-iodophenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
3-[(2-Cyano-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
10 (+/-)-3-[(2-Bromo-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
(+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
15 (+/-)-3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
(+/-)-3-[(2-Acetyl-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
(+/-)-3-[(4,6-Dimethyl-2-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
20 (+/-)-3-[(4,6-Dimethyl-2-methylsulfonylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
(+/-)-3-[(4-Chloro-2-iodo-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
25 3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-phenyl-2(1H)-pyrazinone;
(+/-)-3-[(2,4-Dibromophenyl)amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
30 (+/-)-3-[[2-Bromo-4-(1-methylethyl)phenyl]amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
(+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
35 3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

- 3-[(2,4-Dichloro-6-methylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 3-[(2,4-Dichloro-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 5 3-[(2,4-Dibromo-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- (+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- (+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 10 3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(2-methoxyethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- (+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
- 15 (+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- (+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- (+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 20 (+/-)-3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- (+/-)-3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 25 3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 30 3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 35 (+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

- (+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- (+/-)-3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 5 (+/-)-3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 10 3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 15 (+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-(2-methoxy-1-methylethyl)-2(1H)-pyrazinone;
- (+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-(2-methoxy-1-methylethyl)-2(1H)-pyrazinone;
- 20 (+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(ethoxymethyl)propyl]-2(1H)-pyrazinone;
- (+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-(2-ethoxy-1-methylethyl)-2(1H)-pyrazinone; and
- 25 (+/-)-3-[(4-Bromo-2,6-difluorophenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
- (+/-)-3-[(2-Bromo-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- (+/-)-3-[(2,4-Dimethyl-6-thiomethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 30 (+/-)-3-[(2,4-Dimethyl-6-methylsulfonylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 35 (+/-)-3-[(2,6-Dimethyl-4-(N,N-dimethylamino)phenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

- (+/-)-3-[(2,4-Dichloro-6-methylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- (+/-)-3-[(4-Chloro-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 5 (+/-)-3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- (+/-)-3-[(2,6-Dimethyl-4-methoxyphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 10 (+/-)-3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- (+/-)-3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 15 3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 20 3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 3-[(2,6-Dimethyl-4-(N,N-dimethylamino)phenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 25 3-[(4,6-Dimethyl-2-(N,N-dimethylamino)phenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- (+/-)3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
- 30 (+/-)3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
- (+/-)3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
- 35 (+/-)3-[(4-Bromo-6-methoxy-2-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(4-Bromo-6-methoxy-2-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone; and

3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-(1-ethylpropyl)-2(1H)-pyrazinone.

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[7] A second embodiment of preferred compounds of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

15

Z is CR²;

Y is NR⁴ or O;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵ groups;

20 R¹ is H, halo, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CONR⁶R⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, or -NR⁶R⁷,

25 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl;

30

R² is H, C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl;

R³ is C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl and -NR⁶R⁷,

35

wherein C₁-C₄ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄

haloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷,
-NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷
and -CONR⁶R⁷;

5 R⁴ is H, C₁-C₆ alkyl or C₂-C₆ alkenyl, wherein C₁-C₆ alkyl
is optionally substituted with C₁-C₄ alkyl, C₁-C₄
haloalkyl, -OR⁷, -S(O)_nR¹², -CO₂R⁷, -NR⁶R⁷ or
-NR⁹COR¹⁰;

10 R⁵ is independently selected at each occurrence from
C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆
cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl,
heterocyclyl, -NO₂, halo, -CN, C₁-C₄ haloalkyl,
-NR⁶R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷, -OR⁷, -COR⁷, -CO₂R⁷,
-CONR⁶R⁷, -CON(OR⁹)R⁷ and -S(O)_nR¹³, wherein
15 C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆
cycloalkyl and C₄-C₁₂ cycloalkylalkyl are substituted
with 0 to 3 substituents independently selected at
each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN,
-OR⁷, -COR⁷, -CO₂R⁷, -CONR⁶R⁷, -NR⁶R⁷, -NR⁸COR⁷,
-NR⁸CO₂R⁷ and -S(O)_nR¹³;

20 R⁶ and R⁷ are independently selected at each occurrence
from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-,
heterocyclyl, heterocyclyl (C₁-C₄ alkyl)-,
25 morpholinoethyl, morpholinopropyl and
morpholinobutyl; or -NR⁶R⁷ taken together as a whole
is piperidine, pyrrolidine, piperazine, N-methyl-
piperazine, morpholine or thiomorpholine;
wherein C₁-C₄ alkyl, may be substituted with 0 to 2
30 substituents independently selected at each
occurrence from -OH or C₁-C₄ alkoxy groups;

R⁸ is independently at each occurrence H or C₁-C₄ alkyl;

R⁹ and R¹⁰ are independently at each occurrence selected
from H, C₁-C₄ alkyl and C₃-C₆ cycloalkyl;

35 R¹¹ is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆
cycloalkyl;

R¹² is C₁-C₄ alkyl, C₁-C₄ haloalkyl or -NR⁶R⁷;

- R^{13} is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR⁶R⁷, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-;
- 5 R^{14} is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR¹⁵R¹⁶;
- R^{15} and R^{16} are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl and C₄-
- 10 C₁₂ cycloalkylalkyl; or -NR¹⁵R¹⁶ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;
- aryl is phenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each
- 15 occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵ and -NR¹⁵R¹⁶;
- heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl,
- 20 isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵, and -NR¹⁵R¹⁶; and
- 25 n is independently at each occurrence 0, 1 or 2.

[8] More preferred compounds of the second embodiment of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms

30 thereof, wherein:

- Z is CR²;
- Y is NR⁴;
- Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵
- 35 groups;
- R^1 is H, halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, aryl,

- heterocyclyl, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CONR⁶R⁷, -CO₂R⁷ or -NR⁶R⁷,
wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or C₃-C₆ cycloalkyl is each substituted with 0 to 3
5 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl;
- 10 R² is H;
R³ is C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl and -NR⁶R⁷,
wherein C₁-C₄ alkyl is substituted with 0 to 3
15 substituents independently selected at each occurrence from C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷ and -CONR⁶R⁷;
- 20 R⁴ is H, allyl, or C₁-C₄ alkyl, wherein C₁-C₄ alkyl is optionally substituted with C₁-C₄ alkyl, -OR⁷, -S(O)₂R¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;
- 25 R⁵ is independently selected at each occurrence from C₁-C₆ alkyl, aryl, heterocyclyl, C₁-C₄ haloalkyl, halo, -CN, -NO₂, -NR⁶R⁷, -COR⁷, -OR⁷, -CONR⁶R⁷, -CON(OR⁹)R⁷, -CO₂R⁷ and -S(O)_nR¹³, wherein C₁-C₆ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN, -NR⁶R⁷, COR⁷, -OR⁷, -CONR⁶R⁷, CO₂R⁷ and -S(O)_nR¹³;
- 30 R⁶ and R⁷ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₂-C₈ alkoxyalkyl;
wherein C₁-C₄ alkyl, may be substituted with 0 to 2
35 substituents independently selected at each occurrence from -OH or C₁-C₄ alkoxy groups;
- R⁸, R⁹ and R¹⁰ are independently at each occurrence H or C₁-C₄ alkyl;

R¹² and R¹³ are independently at each occurrence C₁-C₄ alkyl or -NR⁶R⁷;
R¹⁴ is C₁-C₄ alkyl or -NR¹⁵R¹⁶;
R¹⁵ and R¹⁶ are independently at each occurrence H, C₁-C₄ alkyl or C₂-C₈ alkoxyalkyl;
aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂ and -NR¹⁵R¹⁶; and
n is independently at each occurrence 0, 1 or 2.

[10] A third embodiment of preferred compounds of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

Z is N;
Y is NR⁴ or O;
Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵ groups;
R¹ is H, halo, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, aryl, -CN, C₁-C₄ haloalkyl, -NR⁶R⁷, -CONR⁶R⁷, -OR⁷, -COR⁷, -CO₂R⁷ or -S(O)_nR¹³,
wherein C₁-C₄ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₃ alkyl, C₃-C₆ cycloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷, -NR⁶R⁷ and aryl;
R³ is C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -S(O)₂R¹³, -COR⁷, -CO₂R⁷ or -CONR⁶R⁷,
wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -CO₂R⁷,

-NR⁸COR⁷, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, aryl and heterocyclyl;

5 R⁴ is H, C₁-C₆ alkyl or C₂-C₆ alkenyl, wherein C₁-C₆ alkyl is optionally substituted with C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, -OR⁷, -S(O)_nR¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;

10 R⁵ is independently selected at each occurrence from C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₄-C₈ cycloalkylalkyl, aryl, heterocyclyl, C₁-C₄ haloalkyl, halo, -CN, -NO₂, -NR⁶R⁷, -COR⁷, -OR⁷, -CONR⁶R⁷, -CON(OR⁹)R⁷, CO₂R⁷ and -S(O)_nR¹³,

15 wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl and C₄-C₈ cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN, -NR⁶R⁷, COR⁷, -OR⁷, -CONR⁶R⁷, CO₂R⁷ and -S(O)_nR¹³;

20 R⁶ and R⁷ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl, heterocyclyl(C₁-C₄ alkyl)-, morpholinoethyl, morpholinopropyl and
25 morpholinobutyl; or -NR⁶R⁷ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C₁-C₄ alkyl, may be substituted with 0 to 2 substituents independently selected at each
30 occurrence from -OH or C₁-C₄ alkoxy groups;

R⁸ is independently at each occurrence H or C₁-C₄ alkyl;

R⁹ and R¹⁰ are independently at each occurrence selected from H, C₁-C₄ alkyl and C₃-C₆ cycloalkyl;

35 R¹¹ is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;

R¹² is C₁-C₄ alkyl, C₁-C₄ haloalkyl or -NR⁶R⁷;

- R¹³ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR⁶R⁷, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-;
- 5 R¹⁴ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR¹⁵R¹⁶;
R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl and C₄-
10 C₁₂ cycloalkylalkyl; or -NR¹⁵R¹⁶ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;
aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from
15 C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵ and -NR¹⁵R¹⁶;
heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl,
20 isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵, and -NR¹⁵R¹⁶; and
25 n is independently at each occurrence 0, 1 or 2.

[11] More preferred compounds of the third embodiment of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms
30 thereof, wherein:

- Z is N;
Y is NR⁴;
Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵
35 groups;
R¹ is H, halo, C₁-C₄ alkyl, C₁-C₃ haloalkyl, cyclopropyl, -CN, -NR⁶R⁷, -CONR⁶R⁷, -COR⁷, -CO₂R⁷, -OR⁷ or -S(O)_nR¹³

- wherein C₁-C₄ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₃-C₄ cycloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁶R⁷;
- 5 R³ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl or aryl, wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or C₃-C₆ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each
- 10 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -CO₂R⁷, -NR⁸COR⁷, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷ and aryl;
- R⁴ is H, allyl, or C₁-C₄ alkyl, wherein C₁-C₄ alkyl is optionally substituted with C₁-C₄ alkyl, -OR⁷,
- 15 -S(O)₂R¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;
- R⁵ is independently selected at each occurrence from C₁-C₆ alkyl, aryl, heterocyclyl, C₁-C₄ haloalkyl, halo, -CN, -NO₂, -NR⁶R⁷, -COR⁷, -OR⁷, -CONR⁶R⁷, -CON(OR⁹)R⁷, -CO₂R⁷ and -S(O)_nR¹³, wherein C₁-C₆ alkyl
- 20 is substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN, -NR⁶R⁷, COR⁷, -OR⁷, -CONR⁶R⁷, CO₂R⁷ and -S(O)_nR¹³;
- R⁶ and R⁷ are independently selected at each occurrence
- 25 from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₂-C₈ alkoxyalkyl; wherein C₁-C₄ alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C₁-C₄ alkoxy groups;
- 30 R⁸, R⁹ and R¹⁰ are independently at each occurrence H or C₁-C₄ alkyl;
- R¹² and R¹³ are independently at each occurrence C₁-C₄ alkyl or -NR⁶R⁷;
- R¹⁴ is C₁-C₄ alkyl or -NR¹⁵R¹⁶;
- 35 R¹⁵ and R¹⁶ are independently at each occurrence H, C₁-C₄ alkyl or C₂-C₈ alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂ and -NR¹⁵R¹⁶; and

5 n is independently at each occurrence 0, 1 or 2.

[12] Even more preferred compounds of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

10

Z is N;

Y is NR⁴;

Ar is phenyl or pyridyl, each substituted with 2 to 4 R⁵ groups;

15 R¹ is H, methyl, ethyl, cyclopropyl, -CF₃, or -N(CH₃)₂;

R³ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl or aryl, wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or C₃-C₆ cycloalkyl is each substituted with 0 to 3

20 substituents independently selected at each occurrence from C₁-C₄ alkyl, C₃-C₆ cycloalkyl, -CF₃, halo, -CN, -OR⁷, and aryl;

R⁴ is H, methyl, ethyl, i-propyl, n-propyl, n-butyl, i-butyl, s-butyl, n-butyl, or allyl;

25 R⁵ is independently selected at each occurrence from methyl, ethyl, i-propyl, n-propyl, aryl, -CF₃, halo, -CN, -N(CH₃)₂, -C(=O)CH₃, -OCH₃, -OCH₂CH₃, -OCF₃, and -S(O)₂CH₃;

R¹⁴ is C₁-C₄ alkyl or -NR¹⁵R¹⁶;

30 R¹⁵ and R¹⁶ are independently at each occurrence H, C₁-C₄ alkyl or C₂-C₈ alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂ and -NR¹⁵R¹⁶; and

35

n is independently at each occurrence 0, 1 or 2.

[13] A fourth embodiment of preferred compounds of this invention are compounds of Formula (I) and pharmaceutically acceptable salts and pro-drug forms thereof, wherein:

5

Z is N;

Y is NR⁴ or O;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵ groups;

10 R¹ is H, halo, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CONR⁶R⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, or -NR⁶R⁷,

15 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl;

20

R³ is C₁-C₄ alkyl, -CN, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, -OR⁷, -COR⁷, -CO₂R⁷ or -CONR⁶R⁷,

25

wherein C₁-C₄ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷ and -CONR⁶R⁷;

30

R⁴ is H, C₁-C₆ alkyl or C₂-C₆ alkenyl, wherein C₁-C₆ alkyl is optionally substituted with C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, -OR⁷, -S(O)_nR¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;

35

R⁵ is independently selected at each occurrence from C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, heterocyclyl, -NO₂, halo, -CN, C₁-C₄ haloalkyl,

- NR⁶R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷, -OR⁷, -COR⁷, -CO₂R⁷,
-CONR⁶R⁷, -CON(OR⁹)R⁷ and -S(O)_nR¹³,
wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl are
5 substituted with 0 to 3 substituents independently
selected at each occurrence from C₁-C₄ alkyl, -NO₂,
halo, -CN, -OR⁷, -COR⁷, -CO₂R⁷, -CONR⁶R⁷, -NR⁶R⁷,
-NR⁸COR⁷, -NR⁸CO₂R⁷ and -S(O)_nR¹³;
R⁶ and R⁷ are independently selected at each occurrence
10 from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-,
heterocyclyl, heterocyclyl(C₁-C₄ alkyl)-,
morpholinoethyl, morpholinopropyl and
15 morpholinobutyl; or NR⁶R⁷ taken together as a whole is
piperidine, pyrrolidine, piperazine,
N-methylpiperazine, morpholine or thiomorpholine;
wherein C₁-C₄ alkyl, may be substituted with 0 to 2
substituents independently selected at each
20 occurrence from -OH or C₁-C₄ alkoxy groups;
R⁸ is independently at each occurrence H or C₁-C₄ alkyl;
R⁹ and R¹⁰ are independently at each occurrence selected
from H, C₁-C₄ alkyl and C₃-C₆ cycloalkyl;
R¹¹ is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆
25 cycloalkyl;
R¹² is C₁-C₄ alkyl, C₁-C₄ haloalkyl or -NR⁶R⁷;
R¹³ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl,
C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR⁶R⁷,
aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl or
30 heterocyclyl(C₁-C₄ alkyl)-;
R¹⁴ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl,
C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR¹⁵R¹⁶;
R¹⁵ and R¹⁶ are independently selected at each occurrence
from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈
35 alkoxyalkyl, C₃-C₆ cycloalkyl and C₄-
C₁₂ cycloalkylalkyl; or -NR¹⁵R¹⁶ taken together as a

- whole is piperidine, pyrrolidine, piperazine,
N-methyl-piperazine, morpholine or thiomorpholine;
aryl is phenyl or naphthyl, each substituted with 0 to 3
substituents independently selected at each
5 occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵,
-S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵,
-NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵ and -NR¹⁵R¹⁶;
heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl,
thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl,
10 isoxazolyl or pyrazolyl, each substituted with 0 to 3
substituents independently selected at each
occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵,
-S(O)_nR¹⁴, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵, -NR⁸CONR¹⁵R¹⁶,
-NR⁸CO₂R¹⁵, and -NR¹⁵R¹⁶; and
15 n is independently at each occurrence 0, 1 or 2.

- [14] More preferred compounds of the fourth
embodiment of this invention are compounds of Formula (I)
and pharmaceutically acceptable salts and pro-drug forms
20 thereof, wherein:

- Z is N;
Y is NR⁴;
Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵
25 groups;
R¹ is H, halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,
C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, aryl,
heterocyclyl, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CONR⁶R⁷,
-CO₂R⁷ or -NR⁶R⁷,
30 wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or
C₃-C₆ cycloalkyl is each substituted with 0 to 3
substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
C₁-C₄ haloalkyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷,
35 -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷,
-NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl;

- R^3 is C_1 - C_4 alkyl, $-CN$, C_3 - C_6 cycloalkyl, C_1 - C_4 haloalkyl, $-OR^7$, $-COR^7$ or $-CO_2R^7$,
wherein C_1 - C_4 alkyl is substituted with 0 to 3
substituents independently selected at each
occurrence from C_3 - C_6 cycloalkyl, C_1 - C_4 haloalkyl,
halo, $-CN$, $-OR^7$, $-S(O)_nR^{13}$, $-COR^7$, $-CO_2R^7$, $-NR^8COR^7$,
 $-NR^6R^7$ and $-CONR^6R^7$;
 R^4 is H, allyl, or C_1 - C_4 alkyl, wherein C_1 - C_4 alkyl is
optionally substituted with C_1 - C_4 alkyl, $-OR^7$,
 $-S(O)_2R^{12}$, $-CO_2R^7$, $-NR^6R^7$ or $-NR^9COR^{10}$;
 R^5 is independently selected at each occurrence from
 C_1 - C_6 alkyl, aryl, heterocyclyl, C_1 - C_4 haloalkyl,
halo, $-CN$, $-NO_2$, $-NR^6R^7$, $-COR^7$, $-OR^7$, $-CONR^6R^7$,
 $-CON(OR^9)R^7$, $-CO_2R^7$ and $-S(O)_nR^{13}$, wherein C_1 - C_6 alkyl
is substituted with 0 to 3 substituents independently
selected at each occurrence from C_1 - C_4 alkyl, $-NO_2$,
halo, $-CN$, $-NR^6R^7$, COR^7 , $-OR^7$, $-CONR^6R^7$, CO_2R^7 and
 $-S(O)_nR^{13}$;
 R^6 and R^7 are independently selected at each occurrence
from H, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl and C_2 - C_8
alkoxyalkyl;
wherein C_1 - C_4 alkyl, may be substituted with 0 to 2
substituents independently selected at each
occurrence from $-OH$ or C_1 - C_4 alkoxy groups;
 R^8 , R^9 and R^{10} are independently at each occurrence H or
 C_1 - C_4 alkyl;
 R^{12} and R^{13} are independently at each occurrence C_1 - C_4
alkyl or $-NR^6R^7$;
 R^{14} is C_1 - C_4 alkyl or $-NR^{15}R^{16}$;
 R^{15} and R^{16} are independently at each occurrence H, C_1 - C_4
alkyl or C_2 - C_8 alkoxyalkyl;
aryl is phenyl substituted with 0 to 3 substituents
independently selected at each occurrence from
 C_1 - C_4 alkyl, halo, $-CN$, $-OR^{15}$, $-S(O)_nR^{14}$, $-COR^{15}$,
 $-CO_2R^{15}$, $-NO_2$ and $-NR^{15}R^{16}$; and
 n is independently at each occurrence 0, 1 or 2.

A fifth embodiment of this invention is the method of treating affective disorders, anxiety, depression, post-traumatic stress disorders, supranuclear palsy, seizure disorders, stroke, irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other eating disorders, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorders, or fertility problems in a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of a compound of Formula I.

A sixth embodiment of this invention are pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula I.

This invention also includes intermediate compounds useful in preparation of the CRF antagonist compounds and processes for making those intermediates, as described in the following description and claims.

The CRF antagonist compounds provided by this invention (and especially labelled compounds of this invention) are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

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DETAILED DESCRIPTION OF INVENTION

Many compounds of this invention have one or more asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting

materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

5 The term "alkyl" includes both branched and straight-chain alkyl having the specified number of carbon atoms. For example, the term "C₁-C₁₀ alkyl" denotes alkyl having 1 to 10 carbon atoms; thus, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl, wherein, for
10 example, butyl can be -CH₂CH₂CH₂CH₃, -CH₂CH(CH₃)₂, -CH(CH₃)CH₂CH₃ or -CH(CH₃)₃.

 The term "alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any
15 stable point along the chain. For example, the term "C₂-C₁₀ alkenyl" denotes alkenyl having 2 to 10 carbon atoms; thus, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl and decenyl, such as allyl, propargyl, 1-buten-4-yl, 2-buten-4-yl and the like,
20 wherein, for example, butenyl can be, but is not limited to, -CH=CH₂CH₂CH₃, -CH₂CH=CHCH₃, -CH₂CH₂CH=CH₂, -CH=C(CH₃)₂ or -CH=CHCH=CH₂.

 The term "alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more
25 triple carbon-carbon bonds which may occur in any stable point along the chain. The term "C₂-C₁₀ alkynyl" denotes alkynyl having 2 to 10 carbon atoms; thus, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl and decynyl.

30 The term "haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted independently with 1 or more halogen, such as, but not limited to, -CH₂F, -CHF₂, -CF₃, -CF₂Br, -CH₂CF₃, -CF₂CF₃, -CH(CF₃)₂ and the like.

35 The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

The term "cycloalkyl" is intended to include saturated ring groups having the specified number of carbon atoms, including mono-, bi- or poly-cyclic ring systems, such as cyclopropyl (c-Pr), cyclobutyl (c-Bu), cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, [3.3.0]bicyclooctyl, [2.2.2]bicyclooctyl and so forth.

As used herein, the term "heterocyclyl" or "heterocyclic" is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which may be saturated, partially unsaturated, or aromatic, and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Examples of such heterocycles include, but are not limited to, pyridyl (pyridinyl), pyrimidinyl, furanyl (furyl), thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, benzothiophenyl, indolyl, indolenyl, isoxazolinyl, isoxazolyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl or octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thianthrenyl, pyranlyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, 2H-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolinyl, isoxazolyl, oxazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl,

indoliziny1, isoindoly1, 3H-indoly1, indoly1, 1H-indazolyl, puriny1, 4H-quinoliziny1, isoquinoliny1, quinoliny1, phthalaziny1, naphthyridiny1, quinoxaliny1, quinazoliny1, cinnoliny1, pteridiny1, 4aH-carbazole, 5 carbazole, β -carboliny1, phenanthridiny1, acridiny1, perimidiny1, phenanthroliny1, phenaziny1, phenarsaziny1, phenothiaziny1, furazany1, phenoxaziny1, isochromany1, chromany1, pyrrolidiny1, pyrroliny1, imidazolidiny1, imidazoliny1, pyrazolidiny1, pyrazoliny1, piperidiny1, 10 piperaziny1, indoliny1, isoindoliny1, quinuclidiny1, morpholiny1, oxazolidiny1, benzothieny1, 2,3-dihydrobenzofurany1 or 2,3-dihydrobenzothieny1.

The term "halo" or "halogen" includes fluoro, chloro, bromo and iodo.

15 The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a 20 substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is 25 meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "pharmaceutically acceptable salts" includes 30 acid or base salts of the compounds of formula (I). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

35 Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount

of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are
5 found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula
10 (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the
15 parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are
20 not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I); and the like.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to
25 antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

Synthesis

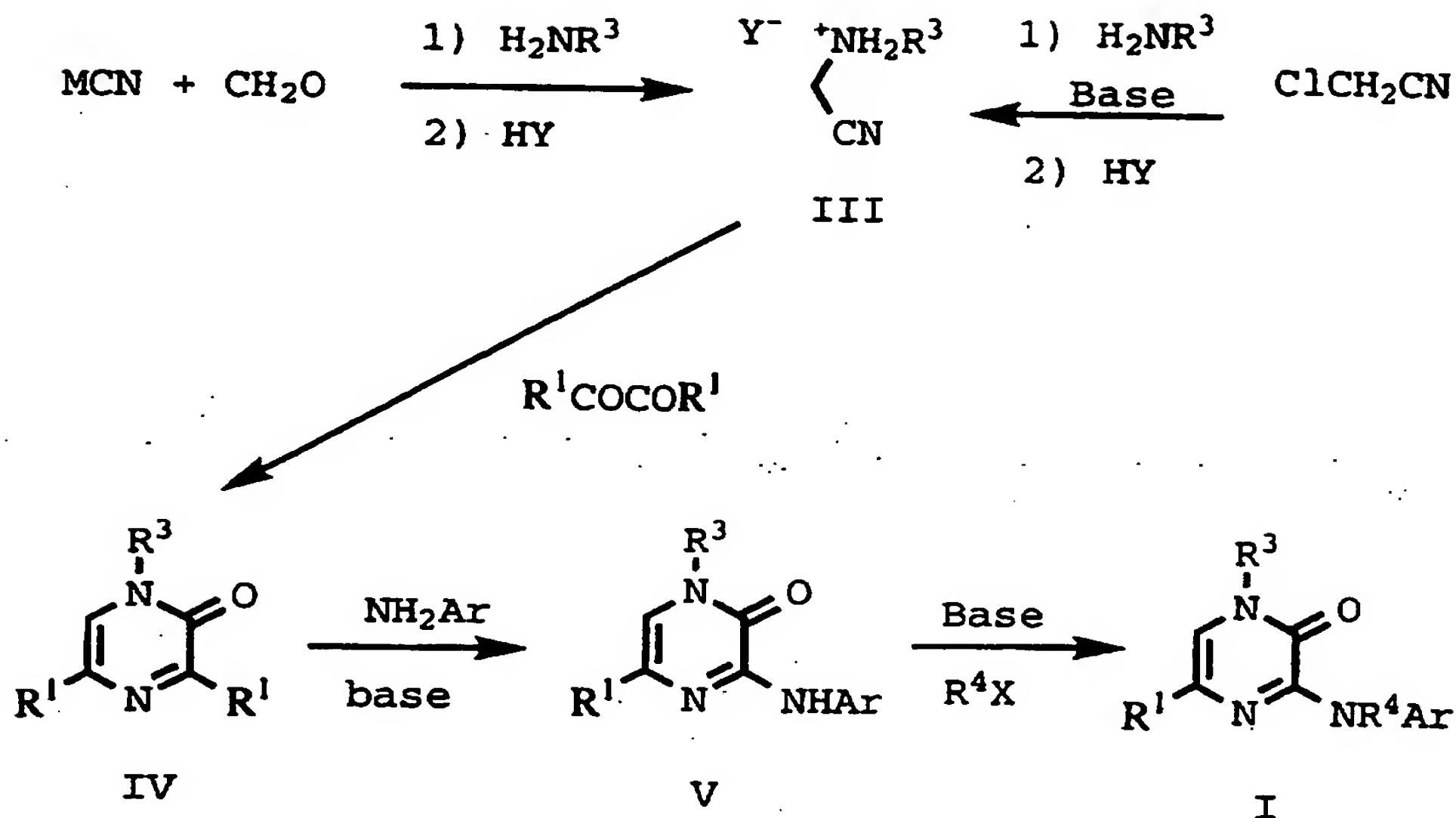
The pyrazinones and triazinones of this invention can
30 be prepared by one of the general schemes outlined below (Scheme 1-6).

Compounds of the Formula (I) wherein $Z = CH$, $Y = NR^4$, $R^1 = \text{halogen}$ and $R^2 = H$ can be prepared as shown in Scheme 1. Compounds wherein R^2 is a substituent other than H as
35 defined in the broad scope of the invention can also be prepared as shown in Scheme 1 by using the corresponding

R^2COH substituted aldehydes or $ClCHR^2CN$ substituted haloacetonitriles.

Scheme 1

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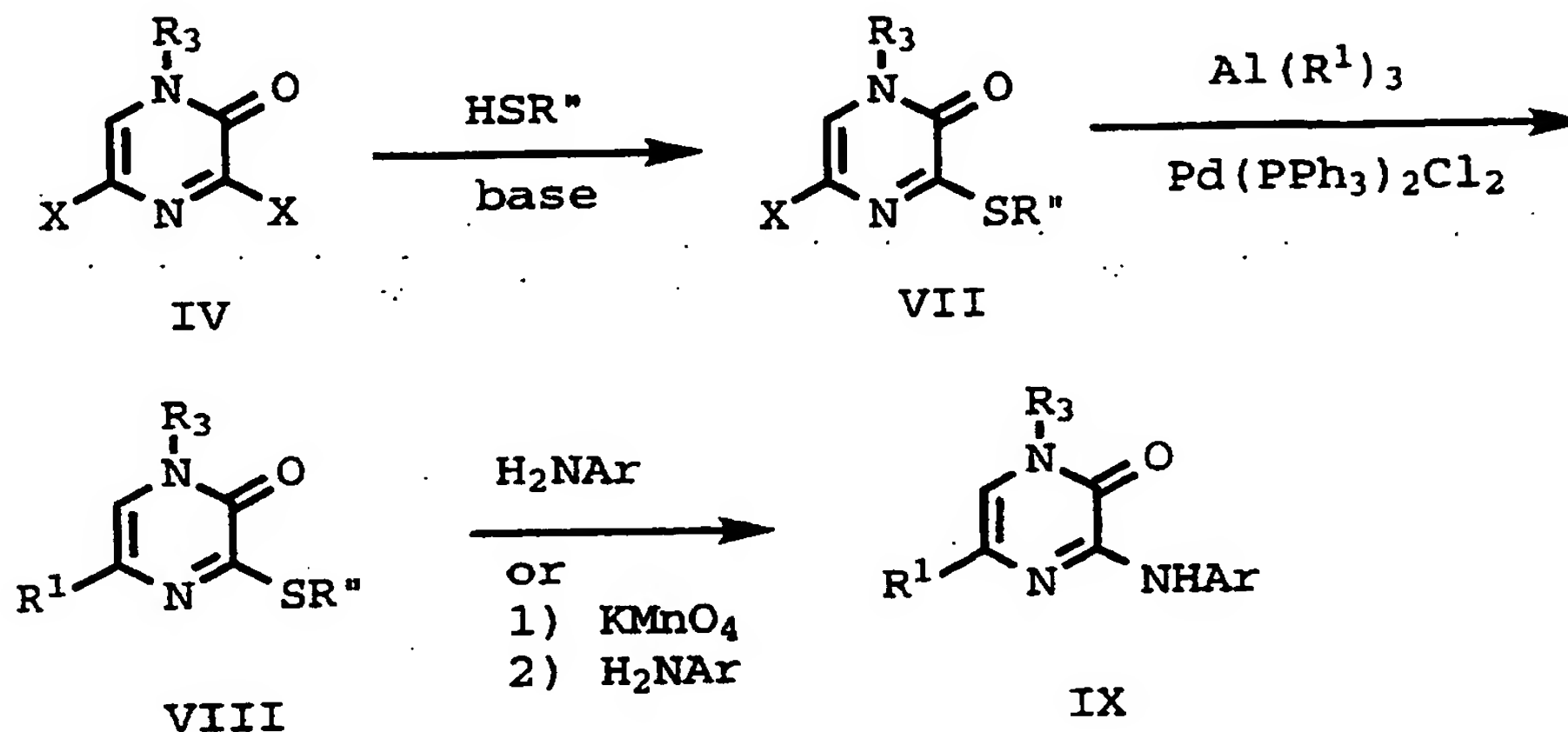
Wherein R¹ = halogen

Reaction of a cyanide salt with formaldehyde and the appropriate substituted amine afforded the corresponding aminoacetonitrile which was purified as the hydrochloride salt of Formula (III). Alternatively the same compounds of Formula (III) can be synthesized by reaction of the amine H_2NR^3 with a haloacetonitrile, such as chloroacetonitrile, in the presence of a base such as a tertiary amine or an inorganic base such as K_2CO_3 in an organic solvent and isolated as a salt of an inorganic acid by treatment with that acid. Amine salt of Formula (III) was treated with an oxalyl halide, R^1COCOR^1 , such as oxalyl chloride or bromide to afford the dihalo compound Formula (IV), as described in Vekemans, J.; Pollers-Wieers, C.; Hoornaert, G. J. *Heterocyclic Chem.* 20, 919, (1982). Compound Formula (IV) can be coupled with an aryl amine H_2NAr thermally, in the presence of a strong base such as NaH , $KN(SiMe_3)_2$, $LiN(SiMe_3)_2$ or $NaN(SiMe_3)_2$ in an aprotic organic solvent,

or under acid catalysis to give compounds of Formula (V).
Compounds of Formula (V) can be alkylated with an alkyl
halide R^4X to afford compounds of Formula (I).

Compounds where R^1 = alkyl or substituted alkyl can be
5 prepared according to Scheme 2.

Scheme 2



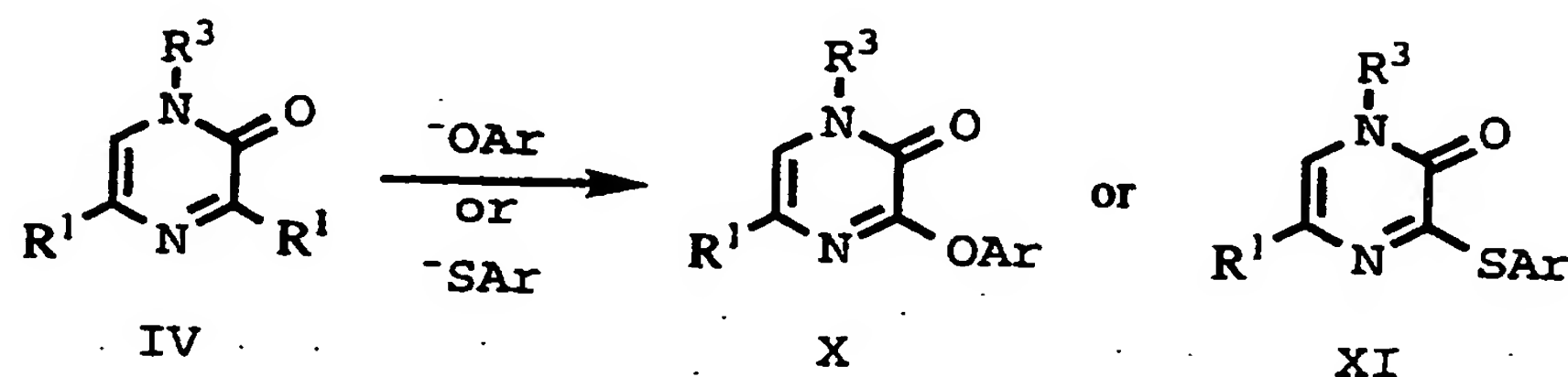
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Reaction of the intermediate of Formula (IV) in Scheme 1,
wherein $R^1 = X$ = halogen in Scheme 2, with an alkyl or aryl
thiol, HSR'' , in the presence of base such as NaH affords
the adduct of Formula (VII), which may then be treated with
15 a trialkylaluminum as described in Hirota, K.; Kitade, Y.;
Kanbe, Y.; Maki, Y.; *J. Org. Chem.* 57, 5268, (1992), in
the presence of a palladium catalyst, such as $Pd(PPh_3)_2Cl_2$,
to give compounds of Formula (VIII). Condensation of
compounds of Formula (VIII) with an aryl amine H_2NAr under
20 thermal, base, or acid catalyzed conditions gives compounds
of Formula (IX). Alternatively (VIII) may be oxidized to
the corresponding sulfones with an oxidant such as $KMnO_4$
and then condensed with the arylamines of formula H_2NAr to
give (IX). The use of appropriately substituted aluminum
25 alkyls, or simple transformations of those substituted
alkyls can give access to compounds of Formula (I), where
 R^1 is a substituted alkyl; see Ratovelomanana,

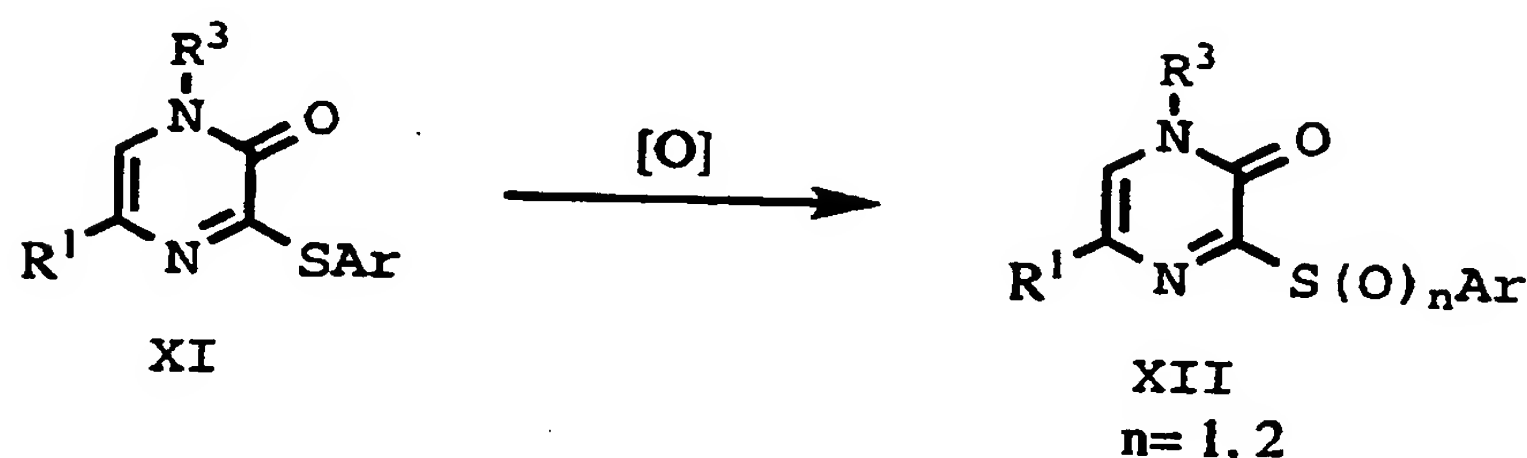
V.; Linstrumelle, G.; *Tet. Letters* 52, 6001 (1984) and references cited therein.

Compounds of the Formula (I) wherein Z = CH, Y = O or S(O)_n and R¹ = halogen can be prepared as shown in Scheme 3.

Scheme 3



Wherein R¹ = halogen



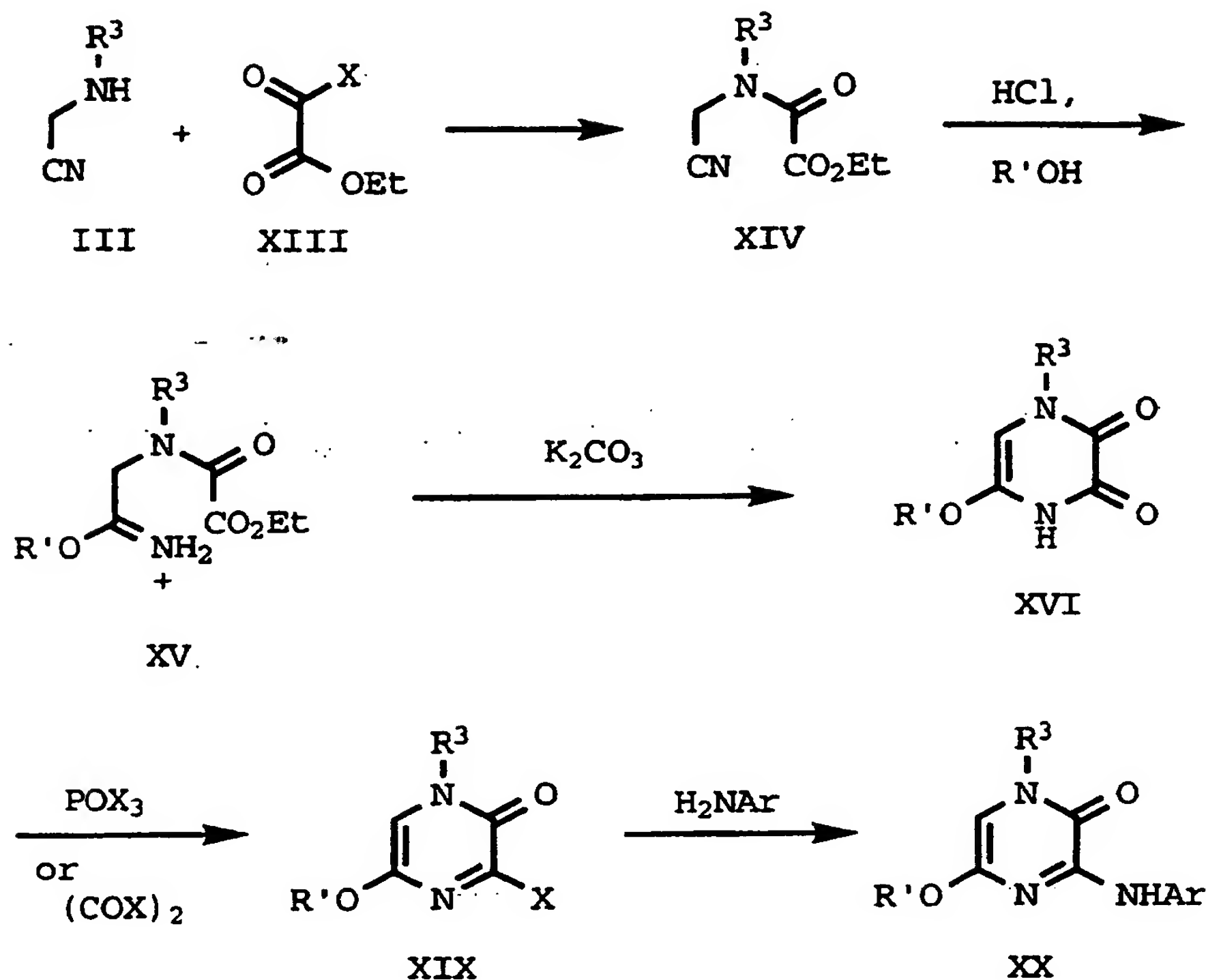
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Reaction of the dihalo intermediate (IV) from Scheme 1 with a phenoxide or thiophenoxide, formed by treatment of the corresponding phenol or thiophenol with an appropriate base, such as NaH in an aprotic solvent, gives the adduct of Formula (X) or (XI). Adduct (XI) may be further oxidized to the sulfoxide or sulfone of Formula (XII), by treatment with the appropriate oxidant, such as a peroxide, NaIO₄ or KMnO₄.

Compounds of Formula (I) where R¹ = OR, SR and S(O)_nR and Z = CH can be introduced on compounds of Formula (V) by copper or copper salt-catalyzed coupling of the corresponding anions RO⁻ and RS⁻ with the pyrazinone bromide. Keegstra, M.A.; Peters, T.H.A.; Brandsma, L.; *Tetrahedron*, 48, 3633 (1992) describes the addition of phenoxide anions by this method; alternatively, the same conditions can be used for the addition of thiophenoxide

anions. Alternatively the same compounds can be synthesized by Scheme 4.

Scheme 4



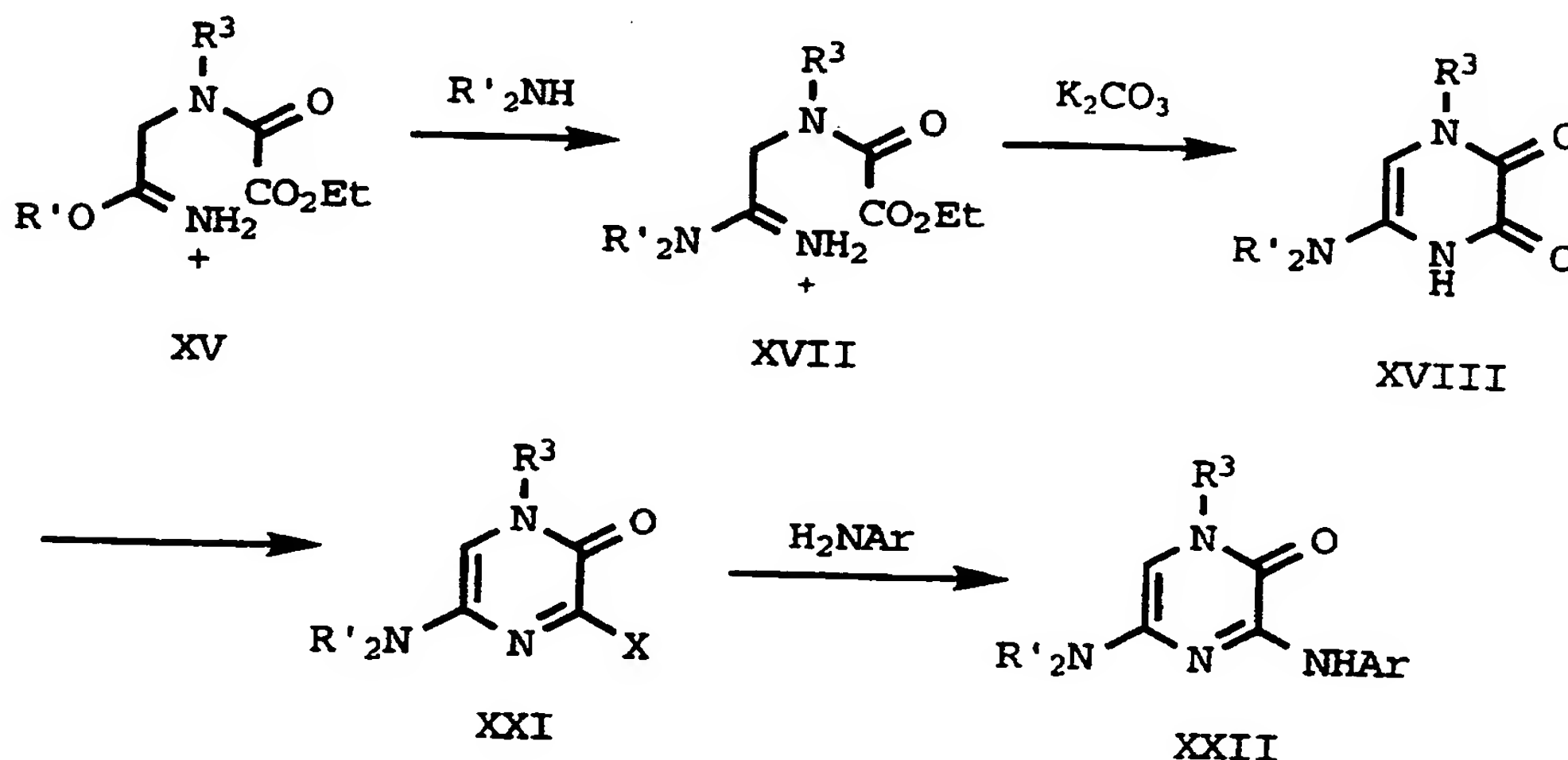
In Scheme 4, reaction of an aminoacetonitrile salt (III), described in Scheme 1, with an oxalyl halide ester (XIII) gives the corresponding amide (XIV), which in turn can be converted to the corresponding imidate salt (XV). This can be cyclized under treatment with a base, such as K_2CO_3 or Et_3N to the pyrazinedione of Formula (XVI). This can be converted to the corresponding halide (XIX), using a halogenating agent such as POX_3 , oxalyl halide or SOX_2 . Alternatively, (XVI) can be converted to the corresponding mesylate, tosylate or triflate, by treatment with the corresponding mesyl, tosyl, or triflic anhydride. Subsequently, (XIX) can be coupled with an aniline to the corresponding adduct of Formula (XX), under the conditions described in Scheme 1, or (XIX) can be coupled with a

phenoxide or thiophenoxide as described in Scheme 3 to yield compounds of Formula (I) wherein $Y = O$ or $S(O)_n$.

Compounds of Formula (I) wherein $R^1 =$ substituted N and $Z = CH$ can be introduced on compounds of Formula (XV) by reaction with an amine to form the corresponding amidate (XVII) according to Scheme 5. Subsequently, (XVII) can be cyclized, halogenated, and substituted with the appropriate aniline, phenoxide or thiophenoxide as described in Scheme 4 above.

Compounds of Formula I wherein $Z = CH$ and $R^1 = COR^7$ or CO_2R^7 can be synthesized from compounds of Formula (VII) by coupling with the appropriate vinyl aluminum or boron reagent in the presence of a palladium catalyst, such as $Pd(PPh_3)_2Cl_2$, and further transformations of the vinyl group, using methods known to one skilled in the art.

Scheme 5



The compounds of Formula (I) where $Z = CH$ and R^1 or R^3 is a functional group not compatible with the procedures of Schemes 1-5 may be prepared from precursors where the interfering functionality of R^1 or R^3 is protected using methods known to one skilled in the art (see T.W. Green and P.G.M. Wuts, *Protecting Groups in Organic Synthesis*, Wiley,

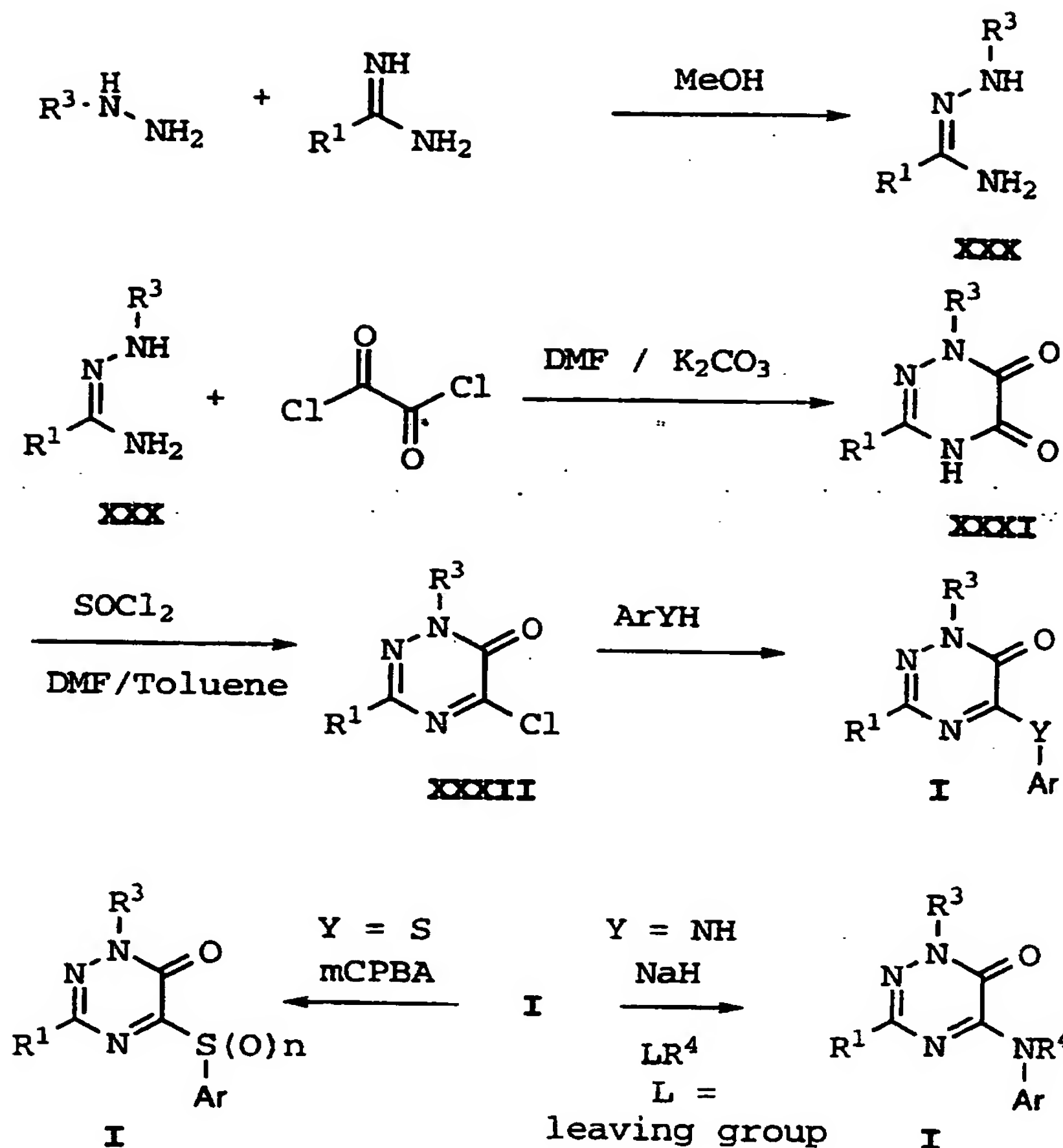
New York, 1991); or from precursors bearing R^1 or R^3 groups amenable to later conversion into the desired functionality using standard methods (see J. March, *Advanced Organic Chemistry*, Wiley, New York, 1992).

5

Triazinones of Formula (I) wherein $Z = N$ and $Y = NR^4$, O or $S(O)_n$ can be prepared by the synthetic route shown in Scheme 6.

- 10 Condensation of a substituted hydrazine with acetamidines or imidates provides amidrazones of Formula (XXX) (Khrustalev, V. A., Zelenin, K. N. Zhurnal Organicheskoi Khimii, Vol. 15, No. 11, 1979, 2280). Cyclization of (XXX) with oxalyl derivatives such as oxalyl chloride provides diones of Formula (XXXI). Treatment of 15 (XXXI) with chlorodehydrating agents such as thionyl chloride, oxalyl chloride or phosphorous oxychloride provides chlorotriazinones of Formula (XXXII), which may be treated with phenols, thiophenols, anilines and their 20 heterocyclic analogs under basic, acidic or thermal conditions to provide compounds of Formula (I) where $Z = N$ and $Y = O$, S or NH , respectively. In the preceding instance where $Y = NH$, alkylation of the nitrogen atom with e.g. alkyl iodides provides the related compounds of 25 Formula (I) where $Z = N$ and $Y = NR^4$. In the preceding instance where $Y = S$, oxidation with e.g. mCPBA provides the compounds of Formula (I) where $Z = N$ and $Y = S(O)$ and $S(O)_2$. The compounds of Formula (I) where $Z = N$ and R^1 or R^3 is a functional group not compatible with the procedures 30 of Scheme 4 may be prepared from precursors such as amidrazones of Formula (XXX) or substituted hydrazines where the

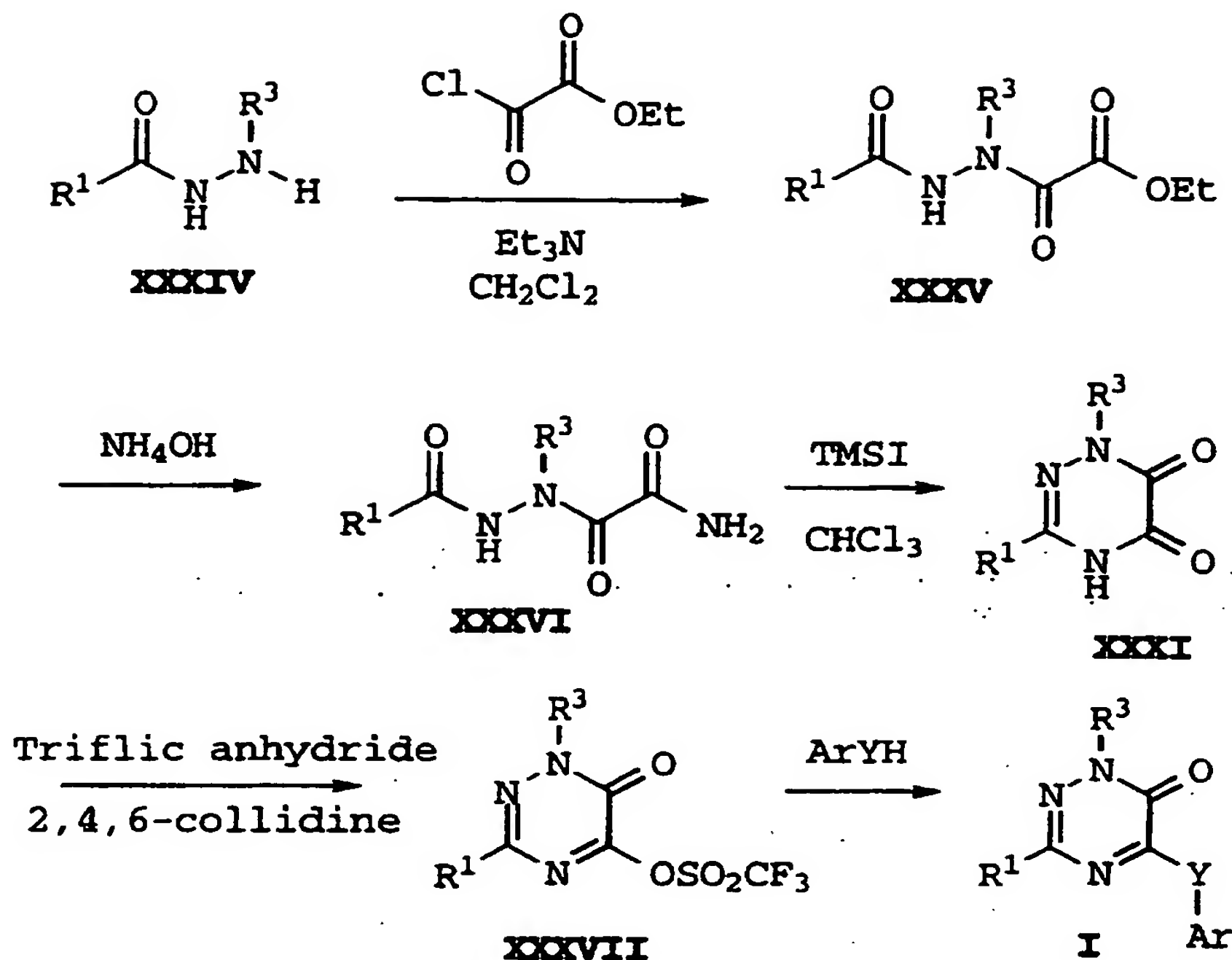
Scheme 6



5
 interfering functionality of R^1 or R^3 is protected using
 methods known to one skilled in the art (see T.W. Green and
 P.G.M. Wuts, *Protecting Groups in Organic Synthesis*, Wiley,
 New York, 1991); or from precursors bearing R^1 or R^3 groups
 10 amenable to later conversion into the desired functionality
 using standard methods (see J. March, *Advanced Organic
 Chemistry*, Wiley, New York, 1992).

15
 Triazinones of Formula (I) wherein $Z = N$ and $Y = NR^4$, O
 or $S(O)_n$ can also be prepared by the synthetic route shown
 in Scheme 7

Scheme 7



5 Reaction of ethyl oxalyl chloride with acylated hydrazines of Formula (XXXIV) provides the ethyl oxalyl acylhydrazine derivatives of Formula (XXXV). Compounds of Formula (XXXIV) may be arrived at via condensation of an appropriate ketone or aldehyde with an acylated hydrazide to

 10 give acylated hydrazones which may then be reduced under catalytic hydrogenation conditions or by other reducing agents to give the compounds of Formula (XXXIV). The abovementioned acylated hydrazones may also be produced by acylation of a hydrazone made from hydrazine and an

 15 appropriate ketone or aldehyde using methods known to one skilled in the art of organic synthesis. Alternatively, compounds of Formula (XXXIV) may also be produced by acylation of an appropriate hydrazine using methods known to one skilled in the art of organic synthesis.

20 The ethyl esters of compound (XXXV) may then be converted to the primary amide derivatives of Formula (XXXVI) by treatment with an ammonia source such as ammonium

hydroxide. Cyclization of (XXXVI) to produce the diones of Formula (XXXI) may be achieved by treatment with, for example, iodotrimethylsilane (TMSI) or POCl₃, or by heating in the presence of a Lewis acid such as ZnCl₂. The oxo group in the 5 position of the 1,2,4-triazin-5,6-diones of Formula (XXXI) may then be converted to a leaving group using reagents such as trifluoromethanesulfonic anhydride under basic conditions to yield compounds of Formula (XXXVII) which may then be treated with phenols, thiophenols, anilines and their heterocyclic analogs under basic conditions to provide compounds of Formula (I)

Additional 1,2,4-triazinone syntheses are disclosed in the literature (A. R. Katritzky and C. W. Rees, *Comprehensive Heterocyclic Chemistry*, Pergamon Press, New York, Vol. 3, 1984, p. 385) and can be prepared by one skilled in the art.

Intermediates, for example ArYH, H₂NAr, HOAr or HSAr, in the synthesis of compounds of Formula (I) in Schemes 1-6 may be prepared using standard methods known to one skilled in the art (see, D. Barton and W. D. Ollis, *Comprehensive Organic Chemistry*, Pergamon Press, New York, Vol. 1-6, 1979; A. R. Katritzky and C. W. Rees, *Comprehensive Heterocyclic Chemistry*, Pergamon Press, New York, Vol. 1-8, 1984; B. Trost and I. Fleming, *Comprehensive Organic Synthesis*, Pergamon Press, New York, Vol. 1-9, 1991; and DuPont Merck PCT application WO95/10506).

All of the aforementioned references are hereby incorporated by reference.

Example 1

3-[[2-Bromo-4-(1-methylethyl)phenyl]amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone

Part A: Hydrogen chloride (12M, aq., 3.8 mL), methanol (33 mL), water (30 mL), potassium cyanide (3 g), 1-ethylpropylamine (4 g), and formaldehyde (37% w/v, 3.7

mL) were stirred 18 hours at room temperature. Water (200 mL) was added, and the mixture was extracted with 2 x 200 mL methylene chloride, which was dried over MgSO₄ and concentrated to a light oil (5.57 g). The oil was
5 dissolved in ether and 1N HCl was added. The precipitate was collected on paper and dried to give N-(1-ethylpropyl)-aminoacetonitrile hydrochloride as an off-white solid (6.70g).

Part B: The product from part A (2 g), chloroform
10 (20 mL), and oxalyl chloride (4.68 g) were heated at reflux for 12 hours. The reaction was concentrated to remove excess oxalyl chloride and solvent, and the crude product was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent to afford 3,5-dichloro-1-(1-ethylpropyl)-2(1H)-pyrazinone as a white solid (2.09 g).
15

Part C: The product from part B (0.68 g) and 2-bromo-4-isopropylaniline (1.24g) were heated at 140°C for 5 hours. After cooling, methylene chloride (20 mL) was added, filtered, and concentrated. The crude product was
20 chromatographed on silica gel using ethyl acetate/hexane (1:9) as eluent to afford the title compound. 639 mg. mp 118.5 - 119.5°C. Elemental analysis: calcd. for C₁₈H₂₃N₃OBrCl: C, 52.38; H, 5.626; N, 10.18; Br, 19.36; Cl, 8.599. Found: C, 52.62; H, 5.43; N, 10.13; Br, 19.53;
25 Cl, 8.97.

Example 2

3-[[2-Bromo-4-(1-methylethyl)phenyl]ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone

30

The product from Example 1 (198 mg), N,N-dimethylformamide (5 mL), and sodium hydride (60% in oil, 96 mg) were stirred at room temperature 20 minutes. Iodoethane (112 mg) was added and the reaction was stirred overnight
35 at room temperature and quenched with water (10 mL) and saturated sodium chloride (aq., 10 mL). The mixture was extracted with methylene chloride which was dried and

concentrated. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:19) as eluent to afford the title compound (125 mg). CI-HRMS calcd. for $C_{20}H_{28}N_3OClBr$ (M+H)⁺: 440.110427. Found: 440.107480.

5

Example 3**3-[(2,4-Dibromophenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone**

10 2,4-Dibromoaniline (500 mg), toluene (8 mL), and sodium hydride (60% in oil, 398 mg) were stirred for 10 minutes at room temperature and then 3,5-dichloro-1-(1-ethylpropyl)-2(1H)-pyrazinone (468 mg, Example 1, part B) was added. The reaction was heated at reflux 3 hours,
15 cooled, and quenched with water (50 mL). The mixture was extracted with ethyl acetate (100 mL), which was washed with brine, then dried and concentrated. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:19) affording 400 mg of material, which
20 was crystallized from ether/hexane to give the title compound (240 mg). Elemental analysis: calcd. for $C_{15}H_{16}N_3OClBr_2$: C, 40.07; H, 3.597; N, 9.356; Cl, 7.895; Br, 35.55. Found: C, 40.41; H, 3.49; N, 9.34; Cl, 8.27; Br, 35.71.

25

Example 4**3-[(2,4-Dibromophenyl)ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone**

30 The title compound was prepared in a manner similar to the product of Example 2. Elemental analysis calcd. for $C_{17}H_{20}N_3OClBr_2$: C, 42.75; H, 4.22; N, 8.807. Found: C, 42.82; H, 4.14; N, 8.67.

35

Example 5**3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone**

The title compound was prepared in a manner similar to the product of Example 3. Elemental analysis calcd. for $C_{18}H_{24}N_3OCl$: C, 64.76; H, 7.256; N, 12.59. Found: C, 64.69; H, 7.03; N, 12.55.

Example 6

3-[(2,4,6-Trimethylphenyl)ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone

10

The title compound was prepared in a manner similar to the product of Example 2. Elemental analysis calcd. for $C_{20}H_{28}N_3OCl$: C, 66.37; H, 7.808; N, 11.61. Found: C, 66.50; H, 7.69; N, 11.51.

15

Example 7

(+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

20

The title compound was prepared in a manner similar to the product of Example 3. Elemental analysis calcd. for $C_{18}H_{24}N_3O_2Cl$: C, 61.80; H, 6.91; N, 12.01; Cl, 10.13. Found: C, 61.69; H, 7.00; N, 11.93; Cl, 9.87.

25

Example 8

3-[(2-Bromo-4,6-dimethoxyphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 3. Elemental analysis calcd. for $C_{17}H_{21}N_3O_3BrCl$: C, 47.40; H, 4.91; N, 9.765. Found: C, 47.06; H, 4.61; N, 9.56.

30

Example 9

3-[(2-Cyano-4,6-dimethylphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone

35

Part A: 3-[(2-Iodo-4,6-dimethylphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone was prepared in a manner similar to Example 3.

Part B: The product from part A (460 mg), N,N-dimethylformamide (8 mL), cuprous cyanide (97 mg), and sodium cyanide were heated at 120°C for 18 hours and then at 130°C for 3 hours. After cooling, ethyl acetate (100 mL) was added to the reaction which was then washed with water (50 mL) and brine (50 mL), dried, and concentrated. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent. The product was then crystallized from methylene chloride/hexane to afford the title compound (235 mg). Elemental analysis calcd. for C₁₈H₂₁N₄OCl: C, 62.69; H, 6.148; N, 16.25; Cl, 10.28. Found: C, 62.29; H, 6.27; N, 15.99; Cl, 10.20.

Example 10

(+/-)-3-[(2-Bromo-4,6-dimethoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 3. Elemental analysis calcd. for C₁₇H₂₁N₃O₄BrCl: C, 45.71; H, 4.748; N, 9.416. Found: C, 45.86; H, 4.43; N, 9.26.

Example 12

(+/-)-3-[(2-Iodo-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

Part A: Chloroacetonitrile (3.2 mL), 2-amino-1-methoxybutane (10.32 g), and deuteriochloroform (50mL) were stirred and heated at reflux for 48 h. Methylene chloride (100 mL) and sodium hydroxide (aq., 1N, 100 mL) were added to the reaction, the layers separated, and the organic layer concentrated to an oil (3.4 g). The oil was dissolved in ether (100 mL) and HCl/ether (1N, 100 mL) was added. The precipitate was collected on paper affording N-

[(1-methoxymethyl)propyl]aminoacetonitrile hydrochloride (6.86 g).

Part B: The title compound was prepared in a manner similar to the product of Example 3. Elemental analysis
5 calcd. for $C_{17}H_{21}N_3O_2Cl$: C, 44.22; H, 4.58; N, 9.10.
Found: C, 44.26; H, 4.60; N, 9.83.

Example 15

**(+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-
10 chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone**

To (+/-)-3,5-dichloro-1-[1-(methoxymethyl)propyl]-
2(1H)-pyrazinone (300 mg) and 4-bromo-2,6-dimethylaniline
(238 mg) in THF (anhydrous, 9.4 mL) at 0°C was added sodium
15 bis(trimethylsilyl)amide (1.0 M/THF, 2.6 mL). The mixture
was stirred at 0°C for 10 minutes. Ethyl acetate (100mL)
was added and washed with water (25 mL) and brine (25 mL).
The organic layer was dried over $MgSO_4$ and concentrated and
the crude product was chromatographed on silica gel using
20 ethyl acetate/hexane (1:4) as eluent. The product was then
crystallized from ethyl acetate/hexane to afford the title
compound (419 mg). Elemental analysis calcd. for
 $C_{17}H_{21}N_3O_2BrCl$: C, 49.23; H, 5.10; N, 10.13. Found: C,
49.33; H, 5.05; N, 10.09.

25

Example 16

**(+/-)-3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-
chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone**

30 To the product of Example 15 (250 mg),
bis(triphenylphosphine)palladium(II) chloride (11 mg), and
tetrakis(triphenylphosphine)palladium(0) (17 mg) in a dry
flask under nitrogen was added toluene (1.5 mL) and 1-
ethoxyvinyl tributyl tin (260 mg). The reaction was heated
35 at reflux 18 hours, and then concentrated *in vacuo*. The
residue was taken up in ether (15 mL) and saturated aqueous
potassium fluoride (15 mL), and filtered. The layers were

separated, and the ether layer was stirred with 1N HCl (aq., 15 mL). The layers were separated and the ether layer was dried over MgSO₄ and concentrated. The crude product was chromatographed on silica gel using ethyl acetate/hexane (3:7) as eluent to afford the title compound (90 mg). Elemental analysis calcd. for C₁₉H₂₄N₃O₃Cl: C, 60.39; H, 6.40; N, 11.12. Found: C, 60.51; H, 6.31; N, 11.00.

10

Example 16a

(+/-)-3-[(4-Acetyl-2-methoxy-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

15

The title compound was prepared in a manner similar to the product of Example 16. Elemental analysis calcd. for C₁₉H₂₄N₃O₄Cl: C, 57.94; H, 6.14; N, 10.67. Found: C, 57.70; H, 5.98; N, 10.41.

20

Example 20

(+/-)-3-[(4-Chloro-2-iodo-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 3. Elemental analysis calcd. for C₁₆H₁₈N₃O₂Cl₂I: C, 39.86; H, 3.76; N, 8.725. Found: C, 40.00; H, 3.69; N, 8.64.

Example 21

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone

Part A: To serinol (9.90 g) in DMF (200 mL) was added triethyl amine (14.6 mL) and then chlorotriphenylmethane (24.3 g). The reaction mixture was stirred at room temperature for 18 hours. Toluene (800 mL) was added and washed with water (500 mL and 250 mL) and brine (250 mL),

and then dried over K₂CO₃ and concentrated to dryness. The product was crytallized from benzene/hexane (1:1) to afford product (14.57 g).

Part B: The product from part A (14.57 g), sodium hydroxide (17.5 g), and iodomethane (8.8 mL) were stirred overnight in DMSO (220 mL) at room temperature. Water (500 mL) was added and extracted with ethyl acetate (3 X 250 mL). The extracts were washed with water (2 X 250 mL) and brine (200 mL), dried over K₂CO₃, and concentrated to give product (14.46 g).

Part C: The product from part B (14.46 g) and hydrogen chloride (1M/Et₂O, 84 mL) were stirred in methanol (300 mL) at room temperature for 6 hours. The solution was washed with hexane (3 X 300 mL), concentrated, and co-evaporated with ethanol affording 2-amino-1,3-methoxypropane (5.69 g).

Part D: The title compound was prepared in a manner similar the product of Example 3. Elemental analysis calcd. for C₁₈H₂₄N₃O₃Cl: C, 59.09; H, 6.61; N, 11.49. Found: C, 59.27; H, 6.53; N, 11.47.

Example 30a

(+/-)-3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 84. Elemental analysis calcd. for C₁₈H₂₄N₃O₂Cl: C, 61.80; H, 6.91; N, 12.01. Found: C, 61.70; H, 6.94; N, 11.56.

Example 36

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd.

for C₁₉H₂₆N₃O₃Cl: C, 60.07; H, 6.908; N, 11.06. Found:
C, 60.22; H, 7.16; N, 10.92.

Example 36a

3-[(4-Bromo-2-methoxy-6-methylphenyl)amino]-5-
5 chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-
pyrazinone

The title compound was prepared in a manner similar
to the product of Example 15. Elemental analysis calcd.
10 for C₁₈H₂₃N₃O₄ClBr: C, 46.92; H, 5.03; N, 9.129. Found:
C, 47.29; H, 5.03; N, 8.98.

Example 45a

3-[(2-Bromo-6-flouro-4-methylphenyl)amino]-5-
15 chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-
pyrazinone

The title compound was prepared in a manner similar
to the product of Example 15. Elemental analysis calcd.
20 for C₁₆H₁₈N₃O₃FClBr: C, 44.21; H, 4.17; N, 9.67. Found:
C, 44.35; H, 4.25; N, 9.41.

Example 46a

3-[(2-Chloro-4-methoxy-6-methylphenyl)amino]-5-
25 chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-
pyrazinone

The title compound was prepared in a manner similar
to the product of Example 15. Elemental analysis calcd.
30 for C₁₇H₂₀N₃O₄Cl₂: C, 50.89; H, 5.02; N, 10.47. Found:
C, 50.72; H, 5.33; N, 10.37.

Example 49

3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-
35 [1-(methoxymethyl)-3-methoxypropyl]-2(1H)-
pyrazinone

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for C₁₈H₂₃N₃O₃ClBr: C, 48.61; H, 5.21; N, 9.457. Found: C, 48.59; H, 5.32; N, 9.45.

5

Example 53

3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone

10 The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for C₁₇H₂₁N₃O₃ClBr: C, 47.40; H, 4.91; N, 9.765. Found: C, 47.52; H, 4.99; N, 9.72.

15

Example 54

3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone

20 The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for C₁₇H₂₁N₃O₃Cl₂: C, 52.86; H, 5.489; N, 10.88. Found: C, 52.89; H, 5.44; N, 10.72.

Example 77

25 **(+/-)-3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone**

30 The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for C₁₈H₂₄N₃O₂ClS: C, 56.62; H, 6.33; N, 11.00; S, 8.405. Found: C, 56.66; H, 6.19; N, 10.89; S, 8.45.

Example 79

35 **(+/-)-3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone**

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for C₁₇H₂₁N₃O₂Cl₂: C, 55.14; H, 5.726; N, 11.35. Found: C, 55.27; H, 5.70; N, 11.25.

5

Example 80

(+/-)-3-[(4-Bromo-6-methoxy-2-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone

10

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for C₁₇H₂₁N₃O₃BrCl: C, 47.40; H, 4.91; N, 9.765. Found: C, 47.91; H, 4.95; N, 9.74.

15

Example 81

3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone

20

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for C₁₈H₂₄N₃O₃ClS: C, 54.33; H, 6.08; N, 10.56; S, 8.06. Found: C, 54.48; H, 6.01; N, 10.46; S, 7.86.

25

Example 83

3-[(4-Bromo-2-methoxy-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone

30

The title compound was prepared in a manner similar to the product of Example 15. Elemental analysis calcd. for C₁₇H₂₁N₃O₄ClBr: C, 45.71; H, 4.748; N, 9.416. Found: C, 45.80; H, 4.70; N, 9.39.

35

Example 84**3-[(2,4,6-Trimethylphenyl)amino]-1-(1-ethylpropyl)-5-methyl-2(1H)-pyrazinone**

5 **Part A:** N-(1-ethylpropyl)aminoacetonitrile hydrochloride (1.41 g) and oxalyl bromide (2.0 M/CH₂Cl₂, 13 mL) were heated at reflux for 18 hours. The reaction was concentrated to remove excess oxalyl bromide and solvent, and the crude product was chromatographed on silica gel
10 using ethyl acetate/hexane (1:4) as eluent to afford 3,5-dibromo-1-(1-ethylpropyl)-2(1H)-pyrazinone as a white solid (1.19 g).

Part B: The product from part A (133 mg) and sodium thiomethoxide (29 mg) were combined in THF (1.5 mL) and
15 stirred at 25 °C 4 hours. More sodium thiomethoxide (29 mg) was added and the reaction was stirred for 2 hours more at room temperature. Water (20 mL) was added and extracted with CH₂Cl₂ (2 X 20 mL). The organic layers were combined, dried over MgSO₄, and concentrated. The crude product was
20 chromatographed on silica gel using ethyl acetate/hexanes (1:4) as eluent to afford 5-bromo-1-(1-ethylpropyl)-3-thiomethyl-2(1H)-pyrazinone (78 mg).

Part C: The product from part B (200 mg) and Pd(PPh₃)₂Cl₂ (40 mg) were combined in dry THF (6 mL) under inert
25 atmosphere (N₂). To that a 2M solution AlMe₃ in hexanes (0.5 mL) was added and the reaction was heated at reflux for one hour. The excess AlMe₃ was quenched with water at 0 °C and the mixture was partitioned between ethyl acetate (50 mL) and water (30 mL). The water was separated and
30 extracted with ethyl acetate (50 mL), and the combined EtOAc extracts were washed with brine, dried (MgSO₄) and stripped in vacuo. The crude product was chromatographed on silica gel using ethyl acetate/hexanes as eluent (1:9) to give 1-(1-ethylpropyl)-5-methyl-3-thiomethyl-2(1H)-
35 pyrazinone (100 mg).

Part D: The product from part B (50 mg) and 2,4,6-trimethylaniline (40 mg) were combined in dry THF (2 mL)

under inert atmosphere (N₂), and cooled to 0 °C. To that a 1M solution NaN(SiMe₃)₂ in THF (0.5 mL) was added dropwise and the reaction was stirred at 0 °C for 20 min. Then an additional NaN(SiMe₃)₂ in THF (0.3 mL) was added and the
5 reaction was stirred at 0 °C for 30 min and at 25 °C for one hour. Then it was quenched with water (30 mL) and extracted with ethyl acetate (80 mL). The ethyl acetate was washed with brine, dried (MgSO₄) and stripped in vacuo. The crude product was chromatographed on silica gel using ethyl
10 acetate/hexanes as eluent (1:9) to give 3-[(2,4,6-trimethylphenyl)amino]-1-(1-ethylpropyl)-5-methyl-2(1H)-pyrazinone (40 mg). mp. 109°C.

Example 84a

15 **3-[(2-Chloro-4,6-dimethylphenyl)amino]-1-(1-ethylpropyl)-5-methyl-2(1H)-pyrazinone**

The title compound was prepared in a manner similar to the product of Example 84. Elemental analysis calcd. for C₁₈H₂₄N₃OCl: C, 64.76; H, 7.256; N, 12.59. Found: C,
20 65.12; H, 7.28; N, 12.33.

Example 84b

25 **3-[(2-Chloro-4-methoxy-6-methylphenyl)amino]-1-(1-ethylpropyl)-5-methyl-2(1H)-pyrazinone**

The title compound was prepared in a manner similar to the product of Example 84. Elemental analysis calcd. for C₁₈H₂₄N₃O₂Cl: C, 61.80; H, 6.91; N, 12.01. Found: C,
30 61.72; H, 6.96; N, 11.83.

Example 84c

35 **3-[(2,4,6-Trimethylphenyl)amino]-1-(1-ethylpropyl)-5-ethyl-2(1H)-pyrazinone**

Part A: 5-bromo-1-(1-ethylpropyl)-3-thiomethyl-2(1H)-pyrazinone was prepared in a manner similar to Example 84, parts A and B.

Part B: To the product of part A (2.14 g) and
5 bis(triphenylphosphine)palladium(II) chloride (258 mg) in anhydrous THF (60 mL) under inert atmosphere was added triethyl aluminum (1 M/THF, 14.7 mL). The reaction was heated at reflux 3 hours and then cooled and quenched with water. Ethyl Acetate (200 mL) was added and washed with
10 water and saturated aqueous sodium chloride. The ethyl acetate was dried over MgSO₄ and concentrated in vacuo. The crude product was chromatographed on silica gel using ethyl acetate/hexane (3:17) as eluent to afford 5-ethyl-1-(1-ethylpropyl)-3-thiomethyl-2(1H)-pyrazinone (809 mg).
15 **Part C:** The title compound was prepared in a manner similar to the product of Example 84 using the product from part B. Elemental analysis calcd. for C₂₀H₂₉N₃O: C, 73.36; H, 8.936; N, 12.83. Found: C, 73.01; H, 8.55; N, 12.69.

20

Example 84d

3-[(2-Chloro-4,6-dimethylphenyl)amino]-1-(1-ethylpropyl)-5-ethyl-2(1H)-pyrazinone

25 The title compound was prepared in a manner similar to the product of Example 84c. Elemental analysis calcd. for C₁₉H₂₆N₃OCl: C, 65.60; H, 7.53; N, 12.08. Found: C, 65.53; H, 7.33; N, 11.92.

30

Example 85

3-[(2,4,6-Trimethylphenyl)amino]-5-bromo-1-(1-ethylpropyl)-2(1H)-pyrazinone

Part A: N-(1-ethylpropyl)-aminoacetonitrile
35 hydrochloride (1.41 g) and oxalyl bromide (2.0 M, CH₂Cl₂, 13 mL) were heated at reflux for 18 hours. The reaction was concentrated to remove excess oxalyl bromide and

solvent, and the crude product was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent to afford 3,5-dibromo-1-(1-ethylpropyl)-2(1H)-pyrazinone as a white solid (1.19 g).

- 5 **Part B:** Using the product of part A, the title compound was prepared in a manner similar to the product of Example 3. MS m/z 378, (m+H)⁺, 100%.

Example 204

- 10 **5-[(2,4,6-Trimethylphenyl)amino]-3-methyl-1-(1-ethylpropyl)-1,2,4-triazine-6(1H)-one**

- 15 **Part A:** 3-Pentanone (18.56 g, 0.215 mol), acetic hydrazide (14.8 g, 0.2 mol), and 200mL of absolute ethanol were placed in a 500mL flask. The reaction mixture was relaxed for 18hr and then evaporated to dryness to afford the desired hydrazone of suitable purity.

- 20 The hydrazone was then dissolved in 200mL of glacial acetic acid containing 1.0 g of PtO₂ and hydrogenated at 50 psi hydrogen pressure for 14 hr. The mixture was decanted from the catalyst and evaporated to dryness to afford 23.9 g of a colorless oil (83% yield for the two steps).

- 25 **Part B:** The 1-acetyl-2-(1-ethylpropyl)hydrazine product from Part A (23.9 g, 0.166 mol) was dissolved in CH₂Cl₂ (200mL) and to the stirring solution was added triethylamine (27.9 mL, 0.2 mol) and ethyl oxalyl chloride (19 mL, 0.17 mol). After stirring at room temperature for 3 hr, the reaction mixture was poured into water and the organic layer was separated, dried (Na₂SO₄), filtered and evaporated in vacuo. To the resultant oil was added ammonium hydroxide (250mL), THF (100mL), and ethanol (50mL). The flask containing the mixture was sealed with a rubber septum and stirred for 18 hr at room temperature. The mixture was then concentrated in vacuo until the reduced volume of solvent remaining was approximately 100mL, and a white precipitate had formed. The flask was then placed in the refrigerator for 1 hr. The precipitate was collected by

vacuum filtration and washed with small volumes of cold water. 26.3 g of a white solid was collected (73% yield). ¹H NMR (300MHz, CDCl₃): δ 7.78 (s, 1H); 6.74 (br s, 1H); 5.6 (br s, 1H); 4.25 (m, 1H); 2.04 (s, 1H); 1.5 (m, 4H); 0.95 (t, 6H, J = 7.3 Hz).

Part C: The 1-oxamyl-1-(3-pentyl)-2-acetylhydrazine product from Part B (2 g, 9.3 mmol) was suspended in chloroform (50mL) and 2 mL of iodotrimethylsilane was added dropwise. The mixture was allowed to stir at room temperature for 12 hr. The reaction mixture was then partitioned between CH₂Cl₂ and 1N NaOH. The aqueous layer was separated and made acidic by addition of conc. HCl and then extracted with CH₂Cl₂. This organic layer was dried (Na₂SO₄), filtered and evaporated in vacuo to yield 1.2 g of an off-white solid of suitable purity (65% yield). ¹H NMR (300MHz, CDCl₃): δ 7.85 (br s, 1H); 4.61 (m, 1H); 2.35 (s, 3H); 1.73 (m, 4H); 0.83 (t, 6H, J = 7.3 Hz).

Part D: To a solution of the triazine dione product from above (198 mg, 1 mmol) in CH₂Cl₂ (5 mL) was added trifluoromethanesulfonic anhydride (0.19 mL, 1.1 mmol) and 2,4,6-collidine (0.15 mL, 1.1 mmol). The resulting reaction mixture was stirred at room temperature for 30 min., then 2,4,6-trimethylaniline (162 mg, 1.2 mmol) in 5 mL of THF was added followed by addition of 2,4,6-collidine (0.15 mL, 1.1 mmol). The resulting reaction mixture was stirred at room temperature for 1 hr, at which time TLC showed complete reaction. The reaction mixture was partitioned between water and CH₂Cl₂. The organic layer was dried (Na₂SO₄), filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel using EtOAc / hexane (1:9) to afford 260 mg of the title compound (83% yield). mp = 133 - 135°C. ¹H NMR (300MHz, CDCl₃): δ 7.89 (br s, 1H); 6.94 (s, 2H); 4.72 (m, 1H); 2.31 (s, 3H); 2.19 (s, 9H); 1.9 - 1.7 (m, 4H); 0.85 (t, 6H, J = 7.32 Hz). Mass Spec. (NH₃-CI): Calc. (M+H)⁺ = 315, Obs. (M+H)⁺ = 315.

Example 703

(+/-)-5-Chloro-1-[1-(methoxymethyl)propyl]-3-(2,4,6-trimethylphenoxy)-2(1H)-pyrazinone

5

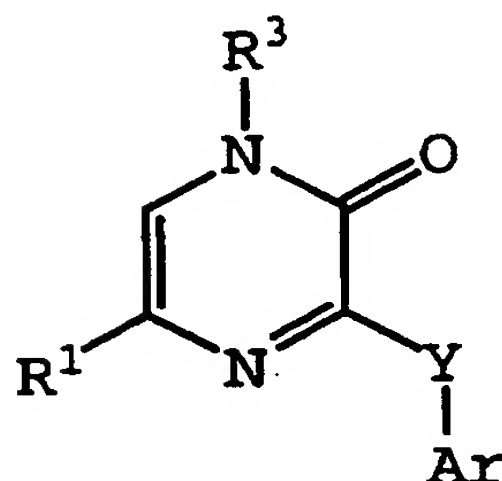
Part A: (+/-)-3,5-dichloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone was prepared in a manner similar to Example 12, part A, and Example 1, part B.

Part B: 2,4,6-Trimethylphenol (59 mg) and potassium t-butoxide (48 mg) were added to pyridine (2 mL) at 0°C. The mixture was warmed to ambient temperature and (+/-)-3,5-dichloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone (98 mg) and copper (I) iodide (19 mg) were added. The reaction mixture was stirred at ambient temperature for three hours and then heated at reflux for three hours and then cooled to 0°C. Ethyl acetate (50 mL) and saturated ammonium chloride (50 mL) were added and the mixture was stirred overnight at ambient temperature. The layers were separated, and the organic layer was washed with 1M ammonium hydroxide (2 x 50 mL), 1N sodium hydroxide (2 x 50mL), 1N hydrochloric acid (2 x 50mL), and saturated sodium chloride (50 mL). The ethyl acetate was dried over MgSO₄ and concentrated in vacuo. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent to afford the title compound (66 mg). mp = 116°C. Elemental analysis calcd. for C₁₈H₂₃N₂O₃Cl: C, 61.62; H, 6.618; N, 7.98. Found: C, 61.45; H, 6.44; N, 7.77.

Various analogs synthesized using Schemes 1, 2 and 3 are listed in Table 1.

Table 1

5



Ex No	R ¹	R ³	Y	Ar	mp / °C
1	Cl	Et ₂ CH	NH	2-Br-4-iPr-phenyl	118.5
2	Cl	Et ₂ CH	NEt	2-Br-4-iPr-phenyl	MS = 440
3	Cl	Et ₂ CH	NH	2,4-Br ₂ -phenyl	155.5
4	Cl	Et ₂ CH	NEt	2,4-Br ₂ -phenyl	88.1
5	Cl	Et ₂ CH	NH	2,4,6-Me ₃ -phenyl	180.8
6	Cl	Et ₂ CH	NEt	2,4,6-Me ₃ -phenyl	93.8
7	Cl	MeOCH ₂ (Et)CH	NH	2,4,6-Me ₃ -phenyl	153.8
8	Cl	Et ₂ CH	NH	2-Br-4,6-(MeO) ₂ -phenyl	181.3
9	Cl	Et ₂ CH	NH	2-CN-4,6-Me ₂ -phenyl	174.0
10	Cl	MeOCH ₂ (Et)CH	NH	2-Br-4,6-(MeO) ₂ -phenyl	175.8
11	Cl	MeOCH ₂ (Et)CH	NH	2-Cl-4,6-(MeO) ₂ -phenyl	
12	Cl	MeOCH ₂ (Et)CH	NH	2-I-4,6-Me ₂ -phenyl	109.4
13	Cl	MeOCH ₂ (Et)CH	NH	2-CN-4,6-Me ₂ -phenyl	
14	Cl	MeOCH ₂ (Et)CH	NH	2-Br-4,6-Me ₂ -phenyl	
15	Cl	MeOCH ₂ (Et)CH	NH	4-Br-2,6-Me ₂ -phenyl	152.8
16	Cl	MeOCH ₂ (Et)CH	NH	4-MeCO-2,6-Me ₂ -phenyl	127.1
16a	Cl	MeOCH ₂ (Et)CH	NH	4-MeCO-2-OMe-6-Me-phenyl	179.8
17	Cl	MeOCH ₂ (Et)CH	NH	2-MeCO-4,6-Me ₂ -phenyl	
18	Cl	MeOCH ₂ (Et)CH	NH	4,6-Me ₂ -2-SMe-phenyl	

19	C1	MeOCH ₂ (Et)CH	NH	4,6-Me ₂ -2-SO ₂ Me-phenyl	
20	C1	MeOCH ₂ (Et)CH	NH	4-Cl-2-I-6-Me-phenyl	121.8
21	C1	(MeOCH ₂) ₂ CH	NH	2,4,6-Me ₃ -phenyl	127.2
22	C1	phenyl	NH	2,4,6-Me ₃ -phenyl	
23	CN	MeOCH ₂ (Et)CH	NH	2,4,6-Me ₃ -phenyl	
24	CONH ₂	MeOCH ₂ (Et)CH	NH	2,4,6-Me ₃ -phenyl	
25	COOH	MeOCH ₂ (Et)CH	NH	2,4,6-Me ₃ -phenyl	
26	CHO	MeOCH ₂ (Et)CH	NH	2,4,6-Me ₃ -phenyl	
27	CH ₂ OH	MeOCH ₂ (Et)CH	NH	2,4,6-Me ₃ -phenyl	
28	CH ₃	MeOCH ₂ (Et)CH	NH	2,4-Br ₂ -phenyl	
29	CH ₃	MeOCH ₂ (Et)CH	NH	2-Br-4-iPr-phenyl	
30	CH ₃	MeOCH ₂ (Et)CH	NH	2,4,6-Me ₃ -phenyl	
30a	CH ₃	MeOCH ₂ (Et)CH	NH	2-Cl-4,6-Me ₂ -phenyl	117.9
31	CH ₃	(MeOCH ₂) ₂ CH	NH	2,4,6-Me ₃ -phenyl	
32	CH ₃	(MeOCH ₂) ₂ CH	NH	2,4-Cl ₂ -6-Me-phenyl	
33	C1	(MeOCH ₂) ₂ CH	NH	2,4-Cl ₂ -6-Me-phenyl	
34	C1	(MeOCH ₂) ₂ CH	NH	2,4-Br ₂ -6-Me-phenyl	
35	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	NH	2,4,6-Me ₃ -phenyl	
36	C1	MeOC ₂ H ₄ (MeOCH ₂)CH	NH	2,4,6-Me ₃ -phenyl	120.0
36a	C1	MeOC ₂ H ₄ (MeOCH ₂)CH	NH	4-Br-2-OMe-6-Me-phenyl	130.9
37	C1	(MeOC ₂ H ₄) ₂ CH	NH	2,4,6-Me ₃ -phenyl	
38	C1	MeOCH ₂ (Et)CH	NH	2,4-Me ₂ -6-MeO-phenyl	
39	C1	MeOC ₂ H ₄ (MeOCH ₂)CH	NH	2,4-Me ₂ -6-MeO-phenyl	
40	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	NH	2,4-Me ₂ -6-MeO-phenyl	
41	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	NH	4-Br-2,6-Me ₂ -phenyl	
42	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	NH	2-Cl-4,6-Me ₂ -phenyl	
43	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	NH	2,4-Me ₂ -6-MeOCH ₂ -phenyl	
44	CH ₃	(MeOCH ₂) ₂ CH	NH	2,4-Me ₂ -6-MeO-phenyl	
45	CH ₃	(MeOCH ₂) ₂ CH	NH	4-Br-2,6-Me ₂ -phenyl	
45a	CH ₃	(MeOCH ₂) ₂ CH	NH	2-Br-6-F-4-Me-phenyl	138.9
46	CH ₃	(MeOCH ₂) ₂ CH	NH	2-Cl-4,6-Me ₂ -phenyl	
46a	CH ₃	(MeOCH ₂) ₂ CH	NH	2-Cl-4-OMe-6-Me-phenyl	128.3
47	CH ₃	(MeOCH ₂) ₂ CH	NH	2,4-Me ₂ -6-MeOCH ₂ -phenyl	

48	Cl	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	2,4-Me ₂ -6-MeO-phenyl	
49	Cl	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	4-Br-2,6-Me ₂ -phenyl	138.6
50	Cl	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	2-Cl-4,6-Me ₂ -phenyl	
51	Cl	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	2,4-Me ₂ -6-MeOCH ₂ - phenyl	
52	Cl	(MeOCH ₂) ₂ CH	NH	2,4-Me ₂ -6-MeO-phenyl	
53	Cl	(MeOCH ₂) ₂ CH	NH	4-Br-2,6-Me ₂ -phenyl	152.1
54	Cl	(MeOCH ₂) ₂ CH	NH	2-Cl-4,6-Me ₂ -phenyl	132.8
55	Cl	(MeOCH ₂) ₂ CH	NH	2,4-Me ₂ -6-MeOCH ₂ - phenyl	
56	Cl	MeOCH ₂ (Me) CH	NH	2,4-Me ₂ -6-MeO-phenyl	
57	Cl	MeOCH ₂ (Me) CH	NH	4-Br-2,6-Me ₂ -phenyl	
58	Cl	EtOCH ₂ (Et) CH	NH	4-Br-2,6-Me ₂ -phenyl	
59	Cl	EtOCH ₂ (Me) CH	NH	4-Br-2,6-Me ₂ -phenyl	
60	Cl	MeOCH ₂ (Et) CH	NH	4-Br-2,6-F ₂ -phenyl	
61	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	2-Br-4,6-Me ₂ -phenyl	
62	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	2,4-Me ₂ -6-SMe-phenyl	
63	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	2,4-Me ₂ -6-SO ₂ Me- phenyl	
64	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	4-NMe ₂ -2,6-Me ₂ - phenyl	
65	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	2,4-Cl ₂ -6-Me-phenyl	
66	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	4-Cl-2,6-Me ₂ -phenyl	
67	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	2,6-Me ₂ -4-SMe-phenyl	
68	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	2,6-Me ₂ -4-OMe-phenyl	
69	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	2,6-Me ₂ -4-SO ₂ Me-phenyl	
70	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	NH	4-MeC(O)-2,6-Me ₂ - phenyl	
71	CH ₃	(MeOCH ₂) ₂ CH	NH	4-Br-2,6-Me ₂ -phenyl	
72	CH ₃	(MeOCH ₂) ₂ CH	NH	4-MeC(O)-2,6-Me ₂ - phenyl	
73	CH ₃	(MeOCH ₂) ₂ CH	NH	2,6-Me ₂ -4-SMe-phenyl	
74	CH ₃	(MeOCH ₂) ₂ CH	NH	2,6-Me ₂ -4-SO ₂ Me-phenyl	
75	CH ₃	(MeOCH ₂) ₂ CH	NH	4-NMe ₂ -2,6-Me ₂ -phenyl	
76	CH ₃	(MeOCH ₂) ₂ CH	NH	2-NMe ₂ -4,6-Me ₂ -phenyl	
77	Cl	MeOCH ₂ (Et) CH	NH	2,6-Me ₂ -4-SMe-phenyl	104.9
78	Cl	MeOCH ₂ (Et) CH	NH	2,6-Me ₂ -4-SO ₂ Me-phenyl	

79	Cl	MeOCH ₂ (Et)CH	NH	2-Cl-4,6-Me ₂ -phenyl	116.7
80	Cl	MeOCH ₂ (Et)CH	NH	4-Br-6-OMe-2-Me-phenyl	147.8
81	Cl	(MeOCH ₂) ₂ CH	NH	2,6-Me ₂ -4-SMe-phenyl	158.9
82	Cl	(MeOCH ₂) ₂ CH	NH	2,6-Me ₂ -4-SO ₂ Me-phenyl	
83	Cl	(MeOCH ₂) ₂ CH	NH	4-Br-6-OMe-2-Me-phenyl	175.5
84	CH ₃	Et ₂ CH	NH	2,4,6-Me ₃ -phenyl	109
84a	CH ₃	Et ₂ CH	NH	2-Cl-4,6-Me ₂ -phenyl	133.8
84b	CH ₃	Et ₂ CH	NH	2-Cl-4-OMe-6-Me-phenyl	121.9
84c	CH ₂ CH ₃	Et ₂ CH	NH	2,4,6-Me ₃ -phenyl	79.3
84d	CH ₂ CH ₃	Et ₂ CH	NH	2-Cl-4,6-Me ₂ -phenyl	95.6
85	Br	Et ₂ CH	NH	2,4,6-Me ₃ -phenyl	MS = 378
86	Br	Et ₂ CH	NH	2-Br-4-iPr-phenyl	
87	Br	Et ₂ CH	NEt	2-Br-4-iPr-phenyl	
88	Br	Et ₂ CH	NH	2,4-Br ₂ -phenyl	
89	Br	Et ₂ CH	NEt	2,4-Br ₂ -phenyl	
90	Br	Et ₂ CH	NEt	2,4,6-Me ₃ -phenyl	
91	Br	Et ₂ CH	NEt	2,4,6-Me ₃ -phenyl	
92	Br	MeOCH ₂ (Et)CH	NH	2,4,6-Me ₃ -phenyl	
93	Br	Et ₂ CH	NH	2-Br-4,6-(MeO) ₂ -phenyl	
94	Br	Et ₂ CH	NH	2-CN-4,6-Me ₂ -phenyl	
95	Br	MeOCH ₂ (Et)CH	NH	2-Br-4,6-(MeO) ₂ -phenyl	
96	Br	MeOCH ₂ (Et)CH	NH	2-I-4,6-Me ₂ -phenyl	
97	Br	MeOCH ₂ (Et)CH	NH	2,6-Me ₂ -4-Br-phenyl	
98	Br	MeOCH ₂ (Et)CH	NH	2-I-4-Cl-6-Me-phenyl	
99	Br	(MeOCH ₂) ₂ CH	NH	2,4,6-Me ₃ -phenyl	
100	Br	MeOCH ₂ (Et)CH	NH	2,6-Me ₂ -4-SMe-phenyl	
101	Br	MeOCH ₂ (Et)CH	NH	2,6-Me ₂ -4-SO ₂ Me-phenyl	
102	Br	MeOCH ₂ (Et)CH	NH	2-Cl-4,6-Me ₂ -phenyl	
103	Br	MeOCH ₂ (Et)CH	NH	2-Me-4-Br-6-OMe-phenyl	
104	CH ₃	Et ₂ CH	NH	2,4,6-Me ₃ -pyrid-3-yl	
105	CH ₃	Et ₂ CH	NH	4,6-Me ₂ -pyrid-3-yl	
106	CH ₃	Et ₂ CH	NH	2-Br-6-Me-pyrid-3-yl	

107	CH ₃	Et ₂ CH	NH	2-Br-6-OMe-pyrid-3-yl
108	CH ₃	Et ₂ CH	NH	2,6-Me ₂ -pyrid-3-yl
109	CH ₃	Et ₂ CH	NH	2-Cl-6-Me-pyrid-3-yl
110	CH ₃	Et ₂ CH	NH	2-Cl-6-OMe-pyrid-3-yl
111	CH ₃	MeOCH ₂ (Et)CH	NH	2,4,6-Me ₃ -pyrid-3-yl
112	CH ₃	MeOCH ₂ (Et)CH	NH	4,6-Me ₂ -pyrid-3-yl
113	CH ₃	MeOCH ₂ (Et)CH	NH	2-Br-6-Me-pyrid-3-yl
114	CH ₃	(MeOCH ₂) ₂ CH	NH	2-Br-6-OMe-pyrid-3-yl
115	CH ₃	(MeOCH ₂) ₂ CH	NH	2,6-Me ₂ -pyrid-3-yl
116	CH ₃	(MeOCH ₂) ₂ CH	NH	2-Cl-6-Me-pyrid-3-yl
117	CH ₃	(MeOCH ₂) ₂ CH	NH	2-Cl-6-OMe-pyrid-3-yl
118	CH ₃	MeOCH ₂ (Et)CH	NH	2-Br-6-OMe-pyrid-3-yl
119	CH ₃	MeOCH ₂ (Et)CH	NH	2,6-Me ₂ -pyrid-3-yl
120	CH ₃	MeOCH ₂ (Et)CH	NH	2-Cl-6-Me-pyrid-3-yl
121	CH ₃	MeOCH ₂ (Et)CH	NH	2-Cl-6-OMe-pyrid-3-yl
120	CH ₃	(MeOCH ₂) ₂ CH	NH	2,4,6-Me ₃ -pyrid-3-yl
123	CH ₃	(MeOCH ₂) ₂ CH	NH	4,6-Me ₂ -pyrid-3-yl
124	CH ₃	(MeOCH ₂) ₂ CH	NH	2-Br-6-Me-pyrid-3-yl
125	Cl	Et ₂ CH	NH	2-Br-6-OMe-pyrid-3-yl
124	Cl	Et ₂ CH	NH	2,6-Me ₂ -pyrid-3-yl
127	Cl	Et ₂ CH	NH	2-Cl-6-Me-pyrid-3-yl
128	Cl	Et ₂ CH	NH	2-Cl-6-OMe-pyrid-3-yl
129	Cl	MeOCH ₂ (Et)CH	NH	2,4,6-Me ₃ -pyrid-3-yl
130	Cl	MeOCH ₂ (Et)CH	NH	4,6-Me ₂ -pyrid-3-yl
131	Cl	MeOCH ₂ (Et)CH	NH	2-Br-6-Me-pyrid-3-yl
132	Cl	Et ₂ CH	NH	2,4,6-Me ₃ -pyrid-3-yl
133	Cl	Et ₂ CH	NH	4,6-Me ₂ -pyrid-3-yl
134	Cl	Et ₂ CH	NH	2-Br-6-Me-pyrid-3-yl
135	Cl	MeOCH ₂ (Et)CH	NH	2-Br-6-OMe-pyrid-3-yl
136	Cl	MeOCH ₂ (Et)CH	NH	2,6-Me ₂ -pyrid-3-yl
137	Cl	MeOCH ₂ (Et)CH	NH	2-Cl-6-Me-pyrid-3-yl
138	Cl	MeOCH ₂ (Et)CH	NH	2-Cl-6-OMe-pyrid-3-yl
139	Cl	(MeOCH ₂) ₂ CH	NH	2-Br-6-OMe-pyrid-3-yl
140	Cl	(MeOCH ₂) ₂ CH	NH	2,6-Me ₂ -pyrid-3-yl
141	Cl	(MeOCH ₂) ₂ CH	NH	2-Cl-6-Me-pyrid-3-yl
142	Cl	(MeOCH ₂) ₂ CH	NH	2-Cl-6-OMe-pyrid-3-yl
143	Cl	(MeOCH ₂) ₂ CH	NH	2,4,6-Me ₃ -pyrid-3-yl

144	Cl	(MeOCH ₂) ₂ CH	NH	4,6-Me ₂ -pyrid-3-yl
145	Cl	(MeOCH ₂) ₂ CH	NH	2-Br-6-Me-pyrid-3-yl
146	Et ₂ CH	CH ₃	NH	2,4,6-Me ₃ -phenyl
147	Et ₂ CH	CH ₃	NH	2,6-Me ₂ -4-Br-phenyl
148	Et ₂ CH	CH ₃	NH	2-Br-4-iPr-phenyl
149	MeOCH ₂ (Et)CH	CH ₃	NH	2,4,6-Me ₃ -phenyl
150	MeOCH ₂ (Et)CH	CH ₃	NH	2,6-Me ₂ -4-Br-phenyl
151	MeOCH ₂ (Et)CH	CH ₃	NH	2-Cl-4,6-Me ₂ -phenyl
152	(MeOCH ₂) ₂ CH	CH ₃	NH	2,4,6-Me ₃ -phenyl
153	(MeOCH ₂) ₂ CH	CH ₃	NH	2,6-Me ₂ -4-Br-phenyl
154	(MeOCH ₂) ₂ CH	CH ₃	NH	2-Cl-4,6-Me ₂ -phenyl
155	Et ₂ CH	CH ₃	NH	2-Br-4,6-(MeO) ₂ -phenyl
156	Et ₂ CH	CH ₃	NH	2-Cl-4,6-Me ₂ -phenyl
400	CH ₃	Me(Et)CH	NH	2,4,6-Me ₃ -phenyl
401	CH ₃	Me(Et)CH	NH	2-Cl-4,6-Me ₂ -phenyl
402	CH ₃	Me(Et)CH	NH	2,4-Cl ₂ -6-Me-phenyl
403	CH ₃	Me(Et)CH	NH	2,4,6-Cl ₃ -phenyl
404	CH ₃	Me(Et)CH	NH	2-Me-4-MeO-phenyl
405	CH ₃	Me(Et)CH	NH	2-Cl-4-MeO-phenyl
406	CH ₃	Me(Et)CH	NH	2,4,6-Me ₃ -5-F-phenyl
407	CH ₃	Me(Et)CH	NH	2,5-Me ₂ -4-MeO-phenyl
408	CH ₃	Me(Et)CH	NH	2,4-Me ₂ -6-MeO-phenyl
409	CH ₃	Me(Et)CH	NH	2,6-Cl ₂ -4-Me-phenyl
410	CH ₃	Me(Et)CH	NH	2,4-Cl ₂ -phenyl
411	CH ₃	Me(Et)CH	NH	2-Cl-4-Me-phenyl
412	CH ₃	Me(Et)CH	NH	2-Me-4-Cl-phenyl
413	CH ₃	Me(Et)CH	NH	2-NMe ₂ -6-Me-pyrid-5-yl
414	CH ₃	Me(Et)CH	NH	2-NMe ₂ -4-Me-pyrid-5-yl
415	CH ₃	Me(Et)CH	NH	2-Cl-4-MeO-6-Me-phenyl
416	CH ₃	Me(Et)CH	NH	2-Cl-4,6-Me ₂ -5-F-phenyl
417	CH ₃	Me(Et)CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
418	CH ₃	Me(Et)CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl

419	CH ₃	Me(n-Pr)CH	NH	2,4,6-Me ₃ -phenyl
420	CH ₃	Me(n-Pr)CH	NH	2-Cl-4,6-Me ₂ -phenyl
421	CH ₃	Me(n-Pr)CH	NH	2,4-Cl ₂ -6-Me-phenyl
422	CH ₃	Me(n-Pr)CH	NH	2,4,6-Cl ₃ -phenyl
423	CH ₃	Me(n-Pr)CH	NH	2-Me-4-MeO-phenyl
424	CH ₃	Me(n-Pr)CH	NH	2-Cl-4-MeO-phenyl
425	CH ₃	Me(n-Pr)CH	NH	2,4,6-Me ₃ -5-F-phenyl
426	CH ₃	Me(n-Pr)CH	NH	2,5-Me ₂ -4-MeO-phenyl
427	CH ₃	Me(n-Pr)CH	NH	2,4-Me ₂ -6-MeO-phenyl
428	CH ₃	Me(n-Pr)CH	NH	2,6-Cl ₂ -4-Me-phenyl
429	CH ₃	Me(n-Pr)CH	NH	2,4-Cl ₂ -phenyl
430	CH ₃	Me(n-Pr)CH	NH	2-Cl-4-Me-phenyl
431	CH ₃	Me(n-Pr)CH	NH	2-Me-4-Cl-phenyl
432	CH ₃	Me(n-Pr)CH	NH	2-NMe ₂ -6-Me-pyrid-5-yl
433	CH ₃	Me(n-Pr)CH	NH	2-NMe ₂ -4-Me-pyrid-5-yl
434	CH ₃	Me(n-Pr)CH	NH	2-Cl-4-MeO-6-Me-phenyl
435	CH ₃	Me(n-Pr)CH	NH	2-Cl-4,6-Me ₂ -5-F-phenyl
436	CH ₃	Me(n-Pr)CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
437	CH ₃	Me(n-Pr)CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl
438	CH ₃	Et ₂ CH	NH	2,4-Cl ₂ -6-Me-phenyl
439	CH ₃	Et ₂ CH	NH	2,4,6-Cl ₃ -phenyl
440	CH ₃	Et ₂ CH	NH	2-Me-4-MeO-phenyl
441	CH ₃	Et ₂ CH	NH	2-Cl-4-MeO-phenyl
442	CH ₃	Et ₂ CH	NH	2,4,6-Me ₃ -5-F-phenyl
443	CH ₃	Et ₂ CH	NH	2,5-Me ₂ -4-MeO-phenyl
444	CH ₃	Et ₂ CH	NH	2,4-Me ₂ -6-MeO-phenyl
445	CH ₃	Et ₂ CH	NH	2,6-Cl ₂ -4-Me-phenyl
446	CH ₃	Et ₂ CH	NH	2,4-Cl ₂ -phenyl
447	CH ₃	Et ₂ CH	NH	2-Cl-4-Me-phenyl
448	CH ₃	Et ₂ CH	NH	2-Me-4-Cl-phenyl
449	CH ₃	Et ₂ CH	NH	2-NMe ₂ -6-Me-pyrid-5-yl
450	CH ₃	Et ₂ CH	NH	2-NMe ₂ -4-Me-pyrid-5-yl
451	CH ₃	Et ₂ CH	NH	2-Cl-4,6-Me ₂ -5-F-phenyl

452	CH ₃	Et ₂ CH	NH	6-Cl-2,3-dihydro- benzofuran-5-yl
453	CH ₃	Et ₂ CH	NH	6-Me-2,3-dihydro- benzofuran-5-yl
454	CH ₃	(c-Pr) ₂ CH	NH	2,4,6-Me ₃ -phenyl
455	CH ₃	(c-Pr) ₂ CH	NH	2-Cl-4,6-Me ₂ -phenyl
456	CH ₃	(c-Pr) ₂ CH	NH	2,4-Cl ₂ -6-Me-phenyl
457	CH ₃	(c-Pr) ₂ CH	NH	2,4,6-Cl ₃ -phenyl
458	CH ₃	(c-Pr) ₂ CH	NH	2-Me-4-MeO-phenyl
459	CH ₃	(c-Pr) ₂ CH	NH	2-Cl-4-MeO-phenyl
460	CH ₃	(c-Pr) ₂ CH	NH	2,4,6-Me ₃ -5-F-phenyl
461	CH ₃	(c-Pr) ₂ CH	NH	2,5-Me ₂ -4-MeO-phenyl
462	CH ₃	(c-Pr) ₂ CH	NH	2,4-Me ₂ -6-MeO-phenyl
463	CH ₃	(c-Pr) ₂ CH	NH	2,6-Cl ₂ -4-Me-phenyl
464	CH ₃	(c-Pr) ₂ CH	NH	2,4-Cl ₂ -phenyl
465	CH ₃	(c-Pr) ₂ CH	NH	2-Cl-4-Me-phenyl
466	CH ₃	(c-Pr) ₂ CH	NH	2-Me-4-Cl-phenyl
467	CH ₃	(c-Pr) ₂ CH	NH	2-NMe ₂ -6-Me-pyrid-5-yl
468	CH ₃	(c-Pr) ₂ CH	NH	2-NMe ₂ -4-Me-pyrid-5-yl
469	CH ₃	(c-Pr) ₂ CH	NH	2-Cl-4-MeO-6-Me-phenyl
470	CH ₃	(c-Pr) ₂ CH	NH	2-Cl-4,6-Me ₂ -5-F- phenyl
471	CH ₃	(c-Pr) ₂ CH	NH	6-Cl-2,3-dihydro- benzofuran-5-yl
472	CH ₃	(c-Pr) ₂ CH	NH	6-Me-2,3-dihydro- benzofuran-5-yl
473	CH ₃	c-Pr(Me)CH	NH	2,4,6-Me ₃ -phenyl
474	CH ₃	c-Pr(Me)CH	NH	2-Cl-4,6-Me ₂ -phenyl
475	CH ₃	c-Pr(Me)CH	NH	2,4-Cl ₂ -6-Me-phenyl
476	CH ₃	c-Pr(Me)CH	NH	2,4,6-Cl ₃ -phenyl
477	CH ₃	c-Pr(Me)CH	NH	2-Me-4-MeO-phenyl
478	CH ₃	c-Pr(Me)CH	NH	2-Cl-4-MeO-phenyl
479	CH ₃	c-Pr(Me)CH	NH	2,4,6-Me ₃ -5-F-phenyl
480	CH ₃	c-Pr(Me)CH	NH	2,5-Me ₂ -4-MeO-phenyl
481	CH ₃	c-Pr(Me)CH	NH	2,4-Me ₂ -6-MeO-phenyl
482	CH ₃	c-Pr(Me)CH	NH	2,6-Cl ₂ -4-Me-phenyl
483	CH ₃	c-Pr(Me)CH	NH	2,4-Cl ₂ -phenyl

484	CH ₃	c-Pr (Me) CH	NH	2-Cl-4-Me-phenyl
485	CH ₃	c-Pr (Me) CH	NH	2-Me-4-Cl-phenyl
486	CH ₃	c-Pr (Me) CH	NH	2-NMe ₂ -6-Me-pyrid-5-yl
487	CH ₃	c-Pr (Me) CH	NH	2-NMe ₂ -4-Me-pyrid-5-yl
488	CH ₃	c-Pr (Me) CH	NH	2-Cl-4-MeO-6-Me-phenyl
489	CH ₃	c-Pr (Me) CH	NH	2-Cl-4,6-Me ₂ -5-F-phenyl
490	CH ₃	c-Pr (Me) CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
491	CH ₃	c-Pr (Me) CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl
492	CH ₃	c-Pr (Et) CH	NH	2,4,6-Me ₃ -phenyl
493	CH ₃	c-Pr (Et) CH	NH	2-Cl-4,6-Me ₂ -phenyl
494	CH ₃	c-Pr (Et) CH	NH	2,4-Cl ₂ -6-Me-phenyl
495	CH ₃	c-Pr (Et) CH	NH	2,4,6-Cl ₃ -phenyl
496	CH ₃	c-Pr (Et) CH	NH	2-Me-4-MeO-phenyl
497	CH ₃	c-Pr (Et) CH	NH	2-Cl-4-MeO-phenyl
498	CH ₃	c-Pr (Et) CH	NH	2,4,6-Me ₃ -5-F-phenyl
499	CH ₃	c-Pr (Et) CH	NH	2,5-Me ₂ -4-MeO-phenyl
500	CH ₃	c-Pr (Et) CH	NH	2,4-Me ₂ -6-MeO-phenyl
501	CH ₃	c-Pr (Et) CH	NH	2,6-Cl ₂ -4-Me-phenyl
502	CH ₃	c-Pr (Et) CH	NH	2,4-Cl ₂ -phenyl
503	CH ₃	c-Pr (Et) CH	NH	2-Cl-4-Me-phenyl
504	CH ₃	c-Pr (Et) CH	NH	2-Me-4-Cl-phenyl
505	CH ₃	c-Pr (Et) CH	NH	2-NMe ₂ -6-Me-pyrid-5-yl
506	CH ₃	c-Pr (Et) CH	NH	2-NMe ₂ -4-Me-pyrid-5-yl
507	CH ₃	c-Pr (Et) CH	NH	2-Cl-4-MeO-6-Me-phenyl
508	CH ₃	c-Pr (Et) CH	NH	2-Cl-4,6-Me ₂ -5-F-phenyl
509	CH ₃	c-Pr (Et) CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
510	CH ₃	c-Pr (Et) CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl
511	CH ₃	c-Pr (n-Pr) CH	NH	2,4,6-Me ₃ -phenyl
512	CH ₃	c-Pr (n-Pr) CH	NH	2-Cl-4,6-Me ₂ -phenyl
513	CH ₃	c-Pr (n-Pr) CH	NH	2,4-Cl ₂ -6-Me-phenyl
514	CH ₃	c-Pr (n-Pr) CH	NH	2,4,6-Cl ₃ -phenyl

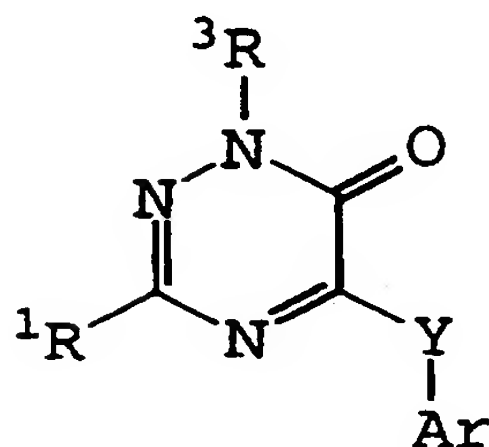
515	CH ₃	c-Pr(n-Pr)CH	NH	2-Me-4-MeO-phenyl
516	CH ₃	c-Pr(n-Pr)CH	NH	2-Cl-4-MeO-phenyl
517	CH ₃	c-Pr(n-Pr)CH	NH	2,4,6-Me ₃ -5-F-phenyl
518	CH ₃	c-Pr(n-Pr)CH	NH	2,5-Me ₂ -4-MeO-phenyl
519	CH ₃	c-Pr(n-Pr)CH	NH	2,4-Me ₂ -6-MeO-phenyl
520	CH ₃	c-Pr(n-Pr)CH	NH	2,6-Cl ₂ -4-Me-phenyl
521	CH ₃	c-Pr(n-Pr)CH	NH	2,4-Cl ₂ -phenyl
522	CH ₃	c-Pr(n-Pr)CH	NH	2-Cl-4-Me-phenyl
523	CH ₃	c-Pr(n-Pr)CH	NH	2-Me-4-Cl-phenyl
524	CH ₃	c-Pr(n-Pr)CH	NH	2-NMe ₂ -6-Me-pyrid-5-yl
525	CH ₃	c-Pr(n-Pr)CH	NH	2-NMe ₂ -4-Me-pyrid-5-yl
526	CH ₃	c-Pr(n-Pr)CH	NH	2-Cl-4-MeO-6-Me-phenyl
527	CH ₃	c-Pr(n-Pr)CH	NH	2-Cl-4,6-Me ₂ -5-F-phenyl
528	CH ₃	c-Pr(n-Pr)CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
529	CH ₃	c-Pr(n-Pr)CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl
530	CH ₃	c-Pr(n-Bu)CH	NH	2,4,6-Me ₃ -phenyl
531	CH ₃	c-Pr(n-Bu)CH	NH	2-Cl-4,6-Me ₂ -phenyl
532	CH ₃	c-Pr(n-Bu)CH	NH	2,4-Cl ₂ -6-Me-phenyl
533	CH ₃	c-Pr(n-Bu)CH	NH	2,4,6-Cl ₃ -phenyl
534	CH ₃	c-Pr(n-Bu)CH	NH	2-Me-4-MeO-phenyl
535	CH ₃	c-Pr(n-Bu)CH	NH	2-Cl-4-MeO-phenyl
536	CH ₃	c-Pr(n-Bu)CH	NH	2,4,6-Me ₃ -5-F-phenyl
537	CH ₃	c-Pr(n-Bu)CH	NH	2,5-Me ₂ -4-MeO-phenyl
538	CH ₃	c-Pr(n-Bu)CH	NH	2,4-Me ₂ -6-MeO-phenyl
539	CH ₃	c-Pr(n-Bu)CH	NH	2,6-Cl ₂ -4-Me-phenyl
540	CH ₃	c-Pr(n-Bu)CH	NH	2,4-Cl ₂ -phenyl
541	CH ₃	c-Pr(n-Bu)CH	NH	2-Cl-4-Me-phenyl
542	CH ₃	c-Pr(n-Bu)CH	NH	2-Me-4-Cl-phenyl
543	CH ₃	c-Pr(n-Bu)CH	NH	2-NMe ₂ -6-Me-pyrid-5-yl
544	CH ₃	c-Pr(n-Bu)CH	NH	2-NMe ₂ -4-Me-pyrid-5-yl
545	CH ₃	c-Pr(n-Bu)CH	NH	2-Cl-4-MeO-6-Me-phenyl
546	CH ₃	c-Pr(n-Bu)CH	NH	2-Cl-4,6-Me ₂ -5-F-phenyl

547	CH ₃	c-Pr (n-Bu) CH	NH	6-Cl-2,3-dihydro- benzofuran-5-yl
548	CH ₃	c-Pr (n-Bu) CH	NH	6-Me-2,3-dihydro- benzofuran-5-yl
549	CH ₃	c-PrCH ₂ (Et) CH	NH	2,4,6-Me ₃ -phenyl
550	CH ₃	c-PrCH ₂ (Et) CH	NH	2-Cl-4,6-Me ₂ -phenyl
551	CH ₃	c-PrCH ₂ (Et) CH	NH	2,4-Cl ₂ -6-Me-phenyl
552	CH ₃	c-PrCH ₂ (Et) CH	NH	2,4,6-Cl ₃ -phenyl
553	CH ₃	c-PrCH ₂ (Et) CH	NH	2-Me-4-MeO-phenyl
554	CH ₃	c-PrCH ₂ (Et) CH	NH	2-Cl-4-MeO-phenyl
555	CH ₃	c-PrCH ₂ (Et) CH	NH	2,4,6-Me ₃ -5-F-phenyl
556	CH ₃	c-PrCH ₂ (Et) CH	NH	2,5-Me ₂ -4-MeO-phenyl
557	CH ₃	c-PrCH ₂ (Et) CH	NH	2,4-Me ₂ -6-MeO-phenyl
558	CH ₃	c-PrCH ₂ (Et) CH	NH	2,6-Cl ₂ -4-Me-phenyl
559	CH ₃	c-PrCH ₂ (Et) CH	NH	2,4-Cl ₂ -phenyl
560	CH ₃	c-PrCH ₂ (Et) CH	NH	2-Cl-4-Me-phenyl
561	CH ₃	c-PrCH ₂ (Et) CH	NH	2-Me-4-Cl-phenyl
562	CH ₃	c-PrCH ₂ (Et) CH	NH	2-NMe ₂ -6-Me-pyrid-5-yl
563	CH ₃	c-PrCH ₂ (Et) CH	NH	2-NMe ₂ -4-Me-pyrid-5-yl
564	CH ₃	c-PrCH ₂ (Et) CH	NH	2-Cl-4-MeO-6-Me-phenyl
565	CH ₃	c-PrCH ₂ (Et) CH	NH	2-Cl-4,6-Me ₂ -5-F- phenyl
566	CH ₃	c-PrCH ₂ (Et) CH	NH	6-Cl-2,3-dihydro- benzofuran-5-yl
567	CH ₃	c-PrCH ₂ (Et) CH	NH	6-Me-2,3-dihydro- benzofuran-5-yl

Compounds that can be synthesized using synthetic Scheme 6 or Scheme 7 are listed in Table 2

Table 2

5



Ex. No.	R ¹	R ³	Y	Ar	mp
200	CH ₃	Et ₂ CH	NH	2,4-Br ₂ -phenyl	
201	CH ₃	Et ₂ CH	NH	2-Br-4-iPr-phenyl	
202	CH ₃	Et ₂ CH	NEt	2,4-Br ₂ -phenyl	
203	CH ₃	Et ₂ CH	NEt	2-Br-4-iPr-phenyl	
204	CH ₃	Et ₂ CH	NH	2,4,6-Me ₃ -phenyl	133
205	CH ₃	Et ₂ CH	NEt	2,4,6-Me ₃ -phenyl	
206	CH ₃	MeOCH ₂ (Et)CH	NH	2,4,6-Me ₃ -phenyl	
207	CH ₃	Et ₂ CH	NH	2-Br-4,6-(MeO) ₂ -phenyl	
208	CH ₃	MeOCH ₂ (Et)CH	NH	2-Br-4,6-(MeO) ₂ -phenyl	
209	CH ₃	MeOCH ₂ (Et)CH	NH	2-Cl-4,6-(MeO) ₂ -phenyl	
210	CH ₃	MeOCH ₂ (Et)CH	NH	2,4-Me ₂ -6-I-phenyl	
211	CH ₃	MeOCH ₂ (Et)CH	NH	2-CN-4,6-Me ₂ -phenyl	
212	CH ₃	MeOCH ₂ (Et)CH	NH	2-Br-4,6-Me ₂ -phenyl	
213	CH ₃	MeOCH ₂ (Et)CH	NH	4-Br-2,6-Me ₂ -phenyl	
214	CH ₃	MeOCH ₂ (Et)CH	NH	4-MeC(O)-2,6-Me ₂ -phenyl	
215	CH ₃	MeOCH ₂ (Et)CH	NH	2-MeC(O)-4,6-Me ₂ -phenyl	
216	CH ₃	MeOCH ₂ (Et)CH	NH	2,4-Me ₂ -6-SMe-phenyl	
217	CH ₃	MeOCH ₂ (Et)CH	NH	2,4-Me ₂ -6-SO ₂ Me-phenyl	
218	CH ₃	MeOCH ₂ (Et)CH	NH	4-Cl-2-I-6-Me-phenyl	
219	CH ₃	(MeOCH ₂) ₂ CH	NH	2,4,6-Me ₃ -phenyl	
220	CH ₃	Et ₂ CH	NH	2,4,6-Me ₃ -phenyl	
221	CH ₃	(MeOCH ₂) ₂ CH	NH	2,4-Cl ₂ -6-Me-phenyl	
222	CH ₃	(MeOCH ₂) ₂ CH	NH	2,4-Br ₂ -6-Me-phenyl	
223	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	NH	2,4,6-Me ₃ -phenyl	

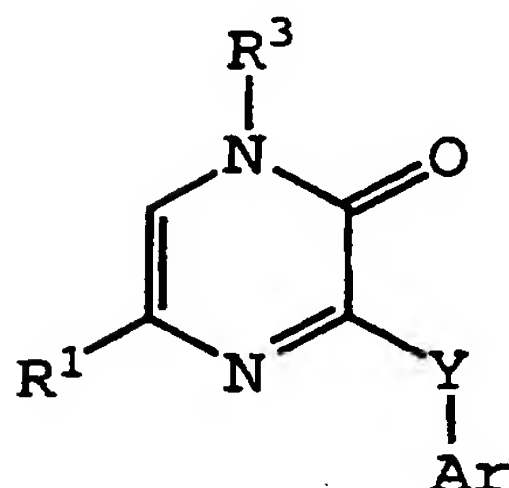
224	CH ₃	(MeOC ₂ H ₄) ₂ CH	NH	2,4,6-Me ₃ -phenyl
225	CH ₃	MeOCH ₂ (Et)CH	NH	2,4-Me ₂ -6-MeO-phenyl
226	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	NH	2,4-Me ₂ -6-MeO-phenyl
227	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	NH	2-Br-4,6-Me ₂ -phenyl
228	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	NH	2-Cl-4,6-Me ₂ -phenyl
229	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	NH	2,4-Me ₂ -6-MeOCH ₂ -phenyl
230	CH ₃	(MeOCH ₂) ₂ CH	NH	2,4-Me ₂ -6-MeO-phenyl
231	CH ₃	(MeOCH ₂) ₂ CH	NH	4-Br-2,6-Me ₂ -phenyl
232	CH ₃	(MeOCH ₂) ₂ CH	NH	2-Cl-4,6-Me ₂ -phenyl
233	CH ₃	(MeOCH ₂) ₂ CH	NH	2,4-Me ₂ -6-MeOCH ₂ -phenyl
234	CH ₃	MeOCH ₂ (Me)CH	NH	2,4-Me ₂ -6-MeO-phenyl
235	CH ₃	MeOCH ₂ (Me)CH	NH	2-Br-4,6-Me ₂ -phenyl
236	CH ₃	EtOCH ₂ (Et)CH	NH	2-Br-4,6-Me ₂ -phenyl
237	CH ₃	EtOCH ₂ (Me)CH	NH	2-Br-4,6-Me ₂ -phenyl
238	CH ₃	MeOCH ₂ (Et)CH	NH	2-Br-4,6-F ₂ -phenyl
239	Et ₂ CH	CH ₃	NH	2,4,6-Me ₃ -phenyl
240	Et ₂ CH	CH ₃	NH	4-Br-2,6-Me ₂ -phenyl
241	Et ₂ CH	CH ₃	NH	2-Br-4-iPr-phenyl
242	MeOCH ₂ (Et)CH	CH ₃	NH	2,4,6-Me ₃ -phenyl
243	MeOCH ₂ (Et)CH	CH ₃	NH	4-Br-2,6-Me ₂ -phenyl
244	MeOCH ₂ (Et)CH	CH ₃	NH	2-Cl-4,6-Me ₂ -phenyl
245	(MeOCH ₂) ₂ CH	CH ₃	NH	2,4,6-Me ₃ -phenyl
246	(MeOCH ₂) ₂ CH	CH ₃	NH	4-Br-2,6-Me ₂ -phenyl
247	(MeOCH ₂) ₂ CH	CH ₃	NH	2-Cl-4,6-Me ₂ -phenyl
248	Et ₂ CH	CH ₃	NH	2-Br-4,6-(MeO) ₂ -phenyl
249	Et ₂ CH	CH ₃	NH	2-Cl-4,6-Me ₂ -phenyl
250	CH ₃	Et ₂ CH	NH	2-Cl-4,6-Me ₂ -phenyl
251	CH ₃	Et ₂ CH	NH	2,4-Cl ₂ -6-Me-phenyl
252	CH ₃	Et ₂ CH	NH	2,4,6-Cl ₃ -phenyl
253	CH ₃	Et ₂ CH	NH	2-Me-4-MeO-phenyl
254	CH ₃	Et ₂ CH	NH	2-Cl-4-MeO-phenyl
255	CH ₃	Et ₂ CH	NH	2,4,6-Me ₃ -5-F-phenyl
256	CH ₃	Et ₂ CH	NH	2,5-Me ₂ -4-MeO-phenyl
257	CH ₃	Et ₂ CH	NH	2,4-Me ₂ -6-MeO-phenyl
258	CH ₃	Et ₂ CH	NH	2,6-Cl ₂ -4-Me-phenyl

259	CH ₃	Et ₂ CH	NH	2,4-Cl ₂ -phenyl
260	CH ₃	Et ₂ CH	NH	2-Cl-4-Me-phenyl
261	CH ₃	Et ₂ CH	NH	2-Me-4-Cl-phenyl
262	CH ₃	Et ₂ CH	NH	2-NMe ₂ -6-Me-pyrid-5-yl
263	CH ₃	Et ₂ CH	NH	2-NMe ₂ -4-Me-pyrid-5-yl
264	CH ₃	Et ₂ CH	NH	2-Cl-4-MeO-6-Me-phenyl
265	CH ₃	Et ₂ CH	NH	2-Cl-4,6-Me ₂ -5-F-phenyl
266	CH ₃	Et ₂ CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
267	CH ₃	Et ₂ CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl
268	CH ₃	MeOCH ₂ (Et)CH	NH	2-Cl-4,6-Me ₂ -phenyl
269	CH ₃	MeOCH ₂ (Et)CH	NH	2,4-Cl ₂ -6-Me-phenyl
270	CH ₃	MeOCH ₂ (Et)CH	NH	2,4,6-Cl ₃ -phenyl
271	CH ₃	MeOCH ₂ (Et)CH	NH	2-Me-4-MeO-phenyl
272	CH ₃	MeOCH ₂ (Et)CH	NH	2-Cl-4-MeO-phenyl
273	CH ₃	MeOCH ₂ (Et)CH	NH	2,4,6-Me ₃ -5-F-phenyl
274	CH ₃	MeOCH ₂ (Et)CH	NH	2,5-Me ₂ -4-MeO-phenyl
275	CH ₃	MeOCH ₂ (Et)CH	NH	2,6-Cl ₂ -4-Me-phenyl
276	CH ₃	MeOCH ₂ (Et)CH	NH	2,4-Cl ₂ -phenyl
277	CH ₃	MeOCH ₂ (Et)CH	NH	2-Cl-4-Me-phenyl
278	CH ₃	MeOCH ₂ (Et)CH	NH	2-Me-4-Cl-phenyl
279	CH ₃	MeOCH ₂ (Et)CH	NH	2-NMe ₂ -6-Me-pyrid-5-yl
280	CH ₃	MeOCH ₂ (Et)CH	NH	2-NMe ₂ -4-Me-pyrid-5-yl
281	CH ₃	MeOCH ₂ (Et)CH	NH	2-Cl-4-MeO-6-Me-phenyl
282	CH ₃	MeOCH ₂ (Et)CH	NH	2-Cl-4,6-Me ₂ -5-F-phenyl
283	CH ₃	MeOCH ₂ (Et)CH	NH	6-Cl-2,3-dihydro-benzofuran-5-yl
284	CH ₃	MeOCH ₂ (Et)CH	NH	6-Me-2,3-dihydro-benzofuran-5-yl

Compounds wherein Y = Oxygen that can be synthesized using synthetic Scheme 3 are listed in Table 3

Table 3

5



Ex No	R ¹	R ³	Y	Ar	mp / °C
700	Cl	Et ₂ CH	O	2-Br-4-iPr-phenyl	
701	Cl	Et ₂ CH	O	2,4-Br ₂ -phenyl	
702	Cl	Et ₂ CH	O	2,4,6-Me ₃ -phenyl	
703	Cl	MeOCH ₂ (Et)CH	O	2,4,6-Me ₃ -phenyl	116
704	Cl	Et ₂ CH	O	2-Br-4,6-(MeO) ₂ -phenyl	
705	Cl	Et ₂ CH	O	2-CN-4,6-Me ₂ -phenyl	
706	Cl	MeOCH ₂ (Et)CH	O	2-Br-4,6-(MeO) ₂ -phenyl	
707	Cl	MeOCH ₂ (Et)CH	O	2-Cl-4,6-(MeO) ₂ -phenyl	
708	Cl	MeOCH ₂ (Et)CH	O	2-I-4,6-Me ₂ -phenyl	
709	Cl	MeOCH ₂ (Et)CH	O	2-CN-4,6-Me ₂ -phenyl	
710	Cl	MeOCH ₂ (Et)CH	O	2-Br-4,6-Me ₂ -phenyl	
711	Cl	MeOCH ₂ (Et)CH	O	4-Br-2,6-Me ₂ -phenyl	
712	Cl	MeOCH ₂ (Et)CH	O	4-MeCO-2,6-Me ₂ -phenyl	
713	Cl	MeOCH ₂ (Et)CH	O	4-MeCO-2-OMe-6-Me-phenyl	
714	Cl	MeOCH ₂ (Et)CH	O	2-MeCO-4,6-Me ₂ -phenyl	
715	Cl	MeOCH ₂ (Et)CH	O	4,6-Me ₂ -2-SMe-phenyl	
716	Cl	MeOCH ₂ (Et)CH	O	4,6-Me ₂ -2-SO ₂ Me-phenyl	
717	Cl	MeOCH ₂ (Et)CH	O	4-Cl-2-I-6-Me-phenyl	
718	Cl	(MeOCH ₂) ₂ CH	O	2,4,6-Me ₃ -phenyl	

719	Cl	phenyl	O	2,4,6-Me ₃ -phenyl
720	CH ₃	MeOCH ₂ (Et)CH	O	2,4-Br ₂ -phenyl
721	CH ₃	MeOCH ₂ (Et)CH	O	2-Br-4-iPr-phenyl
722	CH ₃	MeOCH ₂ (Et)CH	O	2,4,6-Me ₃ -phenyl
723	CH ₃	MeOCH ₂ (Et)CH	O	2-Cl-4,6-Me ₂ -phenyl
724	CH ₃	(MeOCH ₂) ₂ CH	O	2,4,6-Me ₃ -phenyl
725	CH ₃	(MeOCH ₂) ₂ CH	O	2,4-Cl ₂ -6-Me-phenyl
726	Cl	(MeOCH ₂) ₂ CH	O	2,4-Cl ₂ -6-Me-phenyl
727	Cl	(MeOCH ₂) ₂ CH	O	2,4-Br ₂ -6-Me-phenyl
728	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	O	2,4,6-Me ₃ -phenyl
729	Cl	MeOC ₂ H ₄ (MeOCH ₂)CH	O	2,4,6-Me ₃ -phenyl
730	Cl	MeOC ₂ H ₄ (MeOCH ₂)CH	O	4-Br-2-OMe-6-Me-phenyl
731	Cl	(MeOC ₂ H ₄) ₂ CH	O	2,4,6-Me ₃ -phenyl
732	Cl	MeOCH ₂ (Et)CH	O	2,4-Me ₂ -6-MeO-phenyl
733	Cl	MeOC ₂ H ₄ (MeOCH ₂)CH	O	2,4-Me ₂ -6-MeO-phenyl
734	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	O	2,4-Me ₂ -6-MeO-phenyl
735	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	O	4-Br-2,6-Me ₂ -phenyl
736	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	O	2-Cl-4,6-Me ₂ -phenyl
737	CH ₃	MeOC ₂ H ₄ (MeOCH ₂)CH	O	2,4-Me ₂ -6-MeOCH ₂ -phenyl
738	CH ₃	(MeOCH ₂) ₂ CH	O	2,4-Me ₂ -6-MeO-phenyl
739	CH ₃	(MeOCH ₂) ₂ CH	O	4-Br-2,6-Me ₂ -phenyl
740	CH ₃	(MeOCH ₂) ₂ CH	O	2-Br-6-F-4-Me-phenyl
741	CH ₃	(MeOCH ₂) ₂ CH	O	2-Cl-4,6-Me ₂ -phenyl
742	CH ₃	(MeOCH ₂) ₂ CH	O	2-Cl-4-OMe-6-Me-phenyl
743	CH ₃	(MeOCH ₂) ₂ CH	O	2,4-Me ₂ -6-MeOCH ₂ -phenyl
744	Cl	MeOC ₂ H ₄ (MeOCH ₂)CH	O	2,4-Me ₂ -6-MeO-phenyl
745	Cl	MeOC ₂ H ₄ (MeOCH ₂)CH	O	4-Br-2,6-Me ₂ -phenyl
746	Cl	MeOC ₂ H ₄ (MeOCH ₂)CH	O	2-Cl-4,6-Me ₂ -phenyl
747	Cl	MeOC ₂ H ₄ (MeOCH ₂)CH	O	2,4-Me ₂ -6-MeOCH ₂ -phenyl
748	Cl	(MeOCH ₂) ₂ CH	O	2,4-Me ₂ -6-MeO-phenyl
749	Cl	(MeOCH ₂) ₂ CH	O	4-Br-2,6-Me ₂ -phenyl
750	Cl	(MeOCH ₂) ₂ CH	O	2-Cl-4,6-Me ₂ -phenyl

751	Cl	(MeOCH ₂) ₂ CH	O	2,4-Me ₂ -6-MeOCH ₂ -phenyl
752	Cl	MeOCH ₂ (Me) CH	O	2,4-Me ₂ -6-MeO-phenyl
753	Cl	MeOCH ₂ (Me) CH	O	4-Br-2,6-Me ₂ -phenyl
754	Cl	EtOCH ₂ (Et) CH	O	4-Br-2,6-Me ₂ -phenyl
755	Cl	EtOCH ₂ (Me) CH	O	4-Br-2,6-Me ₂ -phenyl
756	Cl	MeOCH ₂ (Et) CH	O	4-Br-2,6-F ₂ -phenyl
757	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	O	2-Br-4,6-Me ₂ -phenyl
758	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	O	2,4-Me ₂ -6-SMe-phenyl
759	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	O	2,4-Me ₂ -6-SO ₂ Me-phenyl
760	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	O	4-NMe ₂ -2,6-Me ₂ -phenyl
761	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	O	2,4-Cl ₂ -6-Me-phenyl
762	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	O	4-Cl-2,6-Me ₂ -phenyl
763	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	O	2,6-Me ₂ -4-SMe-phenyl
764	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	O	2,6-Me ₂ -4-OMe-phenyl
765	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	O	2,6-Me ₂ -4-SO ₂ Me-phenyl
766	CH ₃	MeOC ₂ H ₄ (MeOCH ₂) CH	O	4-MeC(O)-2,6-Me ₂ -phenyl
767	CH ₃	(MeOCH ₂) ₂ CH	O	4-Br-2,6-Me ₂ -phenyl
768	CH ₃	(MeOCH ₂) ₂ CH	O	4-MeC(O)-2,6-Me ₂ -phenyl
769	CH ₃	(MeOCH ₂) ₂ CH	O	2,6-Me ₂ -4-SMe-phenyl
770	CH ₃	(MeOCH ₂) ₂ CH	O	2,6-Me ₂ -4-SO ₂ Me-phenyl
771	CH ₃	(MeOCH ₂) ₂ CH	O	4-NMe ₂ -2,6-Me ₂ -phenyl
772	CH ₃	(MeOCH ₂) ₂ CH	O	2-NMe ₂ -4,6-Me ₂ -phenyl
773	Cl	MeOCH ₂ (Et) CH	O	2,6-Me ₂ -4-SMe-phenyl
774	Cl	MeOCH ₂ (Et) CH	O	2,6-Me ₂ -4-SO ₂ Me-phenyl
775	Cl	MeOCH ₂ (Et) CH	O	2-Cl-4,6-Me ₂ -phenyl
776	Cl	MeOCH ₂ (Et) CH	O	4-Br-6-OMe-2-Me-phenyl
777	Cl	(MeOCH ₂) ₂ CH	O	2,6-Me ₂ -4-SMe-phenyl
778	Cl	(MeOCH ₂) ₂ CH	O	2,6-Me ₂ -4-SO ₂ Me-phenyl
779	Cl	(MeOCH ₂) ₂ CH	O	4-Br-6-OMe-2-Me-phenyl
780	CH ₃	Et ₂ CH	O	2,4,6-Me ₃ -phenyl
781	CH ₃	Et ₂ CH	O	2-Cl-4,6-Me ₂ -phenyl

782	CH ₃	Et ₂ CH	O	2-Cl-4-OMe-6-Me-phenyl
783	CH ₃	Et ₂ CH	O	2,4,6-Me ₃ -pyrid-3-yl
784	CH ₃	Et ₂ CH	O	4,6-Me ₂ -pyrid-3-yl
785	CH ₃	Et ₂ CH	O	2-Br-6-Me-pyrid-3-yl
786	CH ₃	Et ₂ CH	O	2-Br-6-OMe-pyrid-3-yl
787	CH ₃	Et ₂ CH	O	2,6-Me ₂ -pyrid-3-yl
788	CH ₃	Et ₂ CH	O	2-Cl-6-Me-pyrid-3-yl
789	CH ₃	Et ₂ CH	O	2-Cl-6-OMe-pyrid-3-yl
790	CH ₃	MeOCH ₂ (Et)CH	O	2,4,6-Me ₃ -pyrid-3-yl
791	CH ₃	MeOCH ₂ (Et)CH	O	4,6-Me ₂ -pyrid-3-yl
792	CH ₃	MeOCH ₂ (Et)CH	O	2-Br-6-Me-pyrid-3-yl
793	CH ₃	(MeOCH ₂) ₂ CH	O	2-Br-6-OMe-pyrid-3-yl
794	CH ₃	(MeOCH ₂) ₂ CH	O	2,6-Me ₂ -pyrid-3-yl
795	CH ₃	(MeOCH ₂) ₂ CH	O	2-Cl-6-Me-pyrid-3-yl
796	CH ₃	(MeOCH ₂) ₂ CH	O	2-Cl-6-OMe-pyrid-3-yl
797	CH ₃	MeOCH ₂ (Et)CH	O	2-Br-6-OMe-pyrid-3-yl
798	CH ₃	MeOCH ₂ (Et)CH	O	2,6-Me ₂ -pyrid-3-yl
799	CH ₃	MeOCH ₂ (Et)CH	O	2-Cl-6-Me-pyrid-3-yl
800	CH ₃	MeOCH ₂ (Et)CH	O	2-Cl-6-OMe-pyrid-3-yl
801	CH ₃	(MeOCH ₂) ₂ CH	O	2,4,6-Me ₃ -pyrid-3-yl
802	CH ₃	(MeOCH ₂) ₂ CH	O	4,6-Me ₂ -pyrid-3-yl
803	CH ₃	(MeOCH ₂) ₂ CH	O	2-Br-6-Me-pyrid-3-yl
804	Cl	Et ₂ CH	O	2-Br-6-OMe-pyrid-3-yl
805	Cl	Et ₂ CH	O	2,6-Me ₂ -pyrid-3-yl
806	Cl	Et ₂ CH	O	2-Cl-6-Me-pyrid-3-yl
807	Cl	Et ₂ CH	O	2-Cl-6-OMe-pyrid-3-yl
808	Cl	MeOCH ₂ (Et)CH	O	2,4,6-Me ₃ -pyrid-3-yl
809	Cl	MeOCH ₂ (Et)CH	O	4,6-Me ₂ -pyrid-3-yl
810	Cl	MeOCH ₂ (Et)CH	O	2-Br-6-Me-pyrid-3-yl
811	Cl	Et ₂ CH	O	2,4,6-Me ₃ -pyrid-3-yl
812	Cl	Et ₂ CH	O	4,6-Me ₂ -pyrid-3-yl
813	Cl	Et ₂ CH	O	2-Br-6-Me-pyrid-3-yl
814	Cl	MeOCH ₂ (Et)CH	O	2-Br-6-OMe-pyrid-3-yl
815	Cl	MeOCH ₂ (Et)CH	O	2,6-Me ₂ -pyrid-3-yl
816	Cl	MeOCH ₂ (Et)CH	O	2-Cl-6-Me-pyrid-3-yl
817	Cl	MeOCH ₂ (Et)CH	O	2-Cl-6-OMe-pyrid-3-yl

818	Cl	(MeOCH ₂) ₂ CH	O	2-Br-6-OMe-pyrid-3-yl
819	Cl	(MeOCH ₂) ₂ CH	O	2,6-Me ₂ -pyrid-3-yl
820	Cl	(MeOCH ₂) ₂ CH	O	2-Cl-6-Me-pyrid-3-yl
821	Cl	(MeOCH ₂) ₂ CH	O	2-Cl-6-OMe-pyrid-3-yl
822	Cl	(MeOCH ₂) ₂ CH	O	2,4,6-Me ₃ -pyrid-3-yl
823	Cl	(MeOCH ₂) ₂ CH	O	4,6-Me ₂ -pyrid-3-yl
824	Cl	(MeOCH ₂) ₂ CH	O	2-Br-6-Me-pyrid-3-yl
825	CH ₃	Me(Et)CH	O	2,4,6-Me ₃ -phenyl
826	CH ₃	Me(Et)CH	O	2-Cl-4,6-Me ₂ -phenyl
827	CH ₃	Me(Et)CH	O	2,4-Cl ₂ -6-Me-phenyl
828	CH ₃	Me(Et)CH	O	2,4,6-Cl ₃ -phenyl
829	CH ₃	Me(Et)CH	O	2-Me-4-MeO-phenyl
830	CH ₃	Me(Et)CH	O	2-Cl-4-MeO-phenyl
831	CH ₃	Me(Et)CH	O	2,4,6-Me ₃ -5-F-phenyl
832	CH ₃	Me(Et)CH	O	2,5-Me ₂ -4-MeO-phenyl
833	CH ₃	Me(Et)CH	O	2,4-Me ₂ -6-MeO-phenyl
834	CH ₃	Me(Et)CH	O	2,6-Cl ₂ -4-Me-phenyl
835	CH ₃	Me(Et)CH	O	2,4-Cl ₂ -phenyl
836	CH ₃	Me(Et)CH	O	2-Cl-4-Me-phenyl
837	CH ₃	Me(Et)CH	O	2-Me-4-Cl-phenyl
838	CH ₃	Me(Et)CH	O	2-NMe ₂ -6-Me-pyrid-5-yl
839	CH ₃	Me(Et)CH	O	2-NMe ₂ -4-Me-pyrid-5-yl
840	CH ₃	Me(Et)CH	O	2-Cl-4-MeO-6-Me-phenyl
841	CH ₃	Me(Et)CH	O	2-Cl-4,6-Me ₂ -5-F-phenyl
842	CH ₃	Me(Et)CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
843	CH ₃	Me(Et)CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
844	CH ₃	Me(n-Pr)CH	O	2,4,6-Me ₃ -phenyl
845	CH ₃	Me(n-Pr)CH	O	2-Cl-4,6-Me ₂ -phenyl
846	CH ₃	Me(n-Pr)CH	O	2,4-Cl ₂ -6-Me-phenyl
847	CH ₃	Me(n-Pr)CH	O	2,4,6-Cl ₃ -phenyl
848	CH ₃	Me(n-Pr)CH	O	2-Me-4-MeO-phenyl
849	CH ₃	Me(n-Pr)CH	O	2-Cl-4-MeO-phenyl
850	CH ₃	Me(n-Pr)CH	O	2,4,6-Me ₃ -5-F-phenyl
851	CH ₃	Me(n-Pr)CH	O	2,5-Me ₂ -4-MeO-phenyl

852	CH ₃	Me (n-Pr) CH	O	2,4-Me ₂ -6-MeO-phenyl
853	CH ₃	Me (n-Pr) CH	O	2,6-Cl ₂ -4-Me-phenyl
854	CH ₃	Me (n-Pr) CH	O	2,4-Cl ₂ -phenyl
855	CH ₃	Me (n-Pr) CH	O	2-Cl-4-Me-phenyl
856	CH ₃	Me (n-Pr) CH	O	2-Me-4-Cl-phenyl
857	CH ₃	Me (n-Pr) CH	O	2-NMe ₂ -6-Me-pyrid-5-yl
858	CH ₃	Me (n-Pr) CH	O	2-NMe ₂ -4-Me-pyrid-5-yl
859	CH ₃	Me (n-Pr) CH	O	2-Cl-4-MeO-6-Me-phenyl
860	CH ₃	Me (n-Pr) CH	O	2-Cl-4,6-Me ₂ -5-F-phenyl
861	CH ₃	Me (n-Pr) CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
862	CH ₃	Me (n-Pr) CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
863	CH ₃	c-Pr ₂ CH	O	2,4,6-Me ₃ -phenyl
864	CH ₃	c-Pr ₂ CH	O	2-Cl-4,6-Me ₂ -phenyl
865	CH ₃	c-Pr ₂ CH	O	2,4-Cl ₂ -6-Me-phenyl
866	CH ₃	c-Pr ₂ CH	O	2,4,6-Cl ₃ -phenyl
867	CH ₃	c-Pr ₂ CH	O	2-Me-4-MeO-phenyl
868	CH ₃	c-Pr ₂ CH	O	2-Cl-4-MeO-phenyl
869	CH ₃	c-Pr ₂ CH	O	2,4,6-Me ₃ -5-F-phenyl
870	CH ₃	c-Pr ₂ CH	O	2,5-Me ₂ -4-MeO-phenyl
871	CH ₃	c-Pr ₂ CH	O	2,4-Me ₂ -6-MeO-phenyl
872	CH ₃	c-Pr ₂ CH	O	2,6-Cl ₂ -4-Me-phenyl
873	CH ₃	c-Pr ₂ CH	O	2,4-Cl ₂ -phenyl
874	CH ₃	c-Pr ₂ CH	O	2-Cl-4-Me-phenyl
875	CH ₃	c-Pr ₂ CH	O	2-Me-4-Cl-phenyl
876	CH ₃	c-Pr ₂ CH	O	2-NMe ₂ -6-Me-pyrid-5-yl
877	CH ₃	c-Pr ₂ CH	O	2-NMe ₂ -4-Me-pyrid-5-yl
878	CH ₃	c-Pr ₂ CH	O	2-Cl-4-MeO-6-Me-phenyl
879	CH ₃	c-Pr ₂ CH	O	2-Cl-4,6-Me ₂ -5-F-phenyl
880	CH ₃	c-Pr ₂ CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
881	CH ₃	c-Pr ₂ CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
882	CH ₃	c-Pr (Me) CH	O	2,4,6-Me ₃ -phenyl

883	CH ₃	c-Pr (Me) CH	O	2-Cl-4,6-Me ₂ -phenyl
884	CH ₃	c-Pr (Me) CH	O	2,4-Cl ₂ -6-Me-phenyl
885	CH ₃	c-Pr (Me) CH	O	2,4,6-Cl ₃ -phenyl
886	CH ₃	c-Pr (Me) CH	O	2-Me-4-MeO-phenyl
887	CH ₃	c-Pr (Me) CH	O	2-Cl-4-MeO-phenyl
888	CH ₃	c-Pr (Me) CH	O	2,4,6-Me ₃ -5-F-phenyl
889	CH ₃	c-Pr (Me) CH	O	2,5-Me ₂ -4-MeO-phenyl
890	CH ₃	c-Pr (Me) CH	O	2,4-Me ₂ -6-MeO-phenyl
891	CH ₃	c-Pr (Me) CH	O	2,6-Cl ₂ -4-Me-phenyl
892	CH ₃	c-Pr (Me) CH	O	2,4-Cl ₂ -phenyl
893	CH ₃	c-Pr (Me) CH	O	2-Cl-4-Me-phenyl
894	CH ₃	c-Pr (Me) CH	O	2-Me-4-Cl-phenyl
895	CH ₃	c-Pr (Me) CH	O	2-NMe ₂ -6-Me-pyrid-5-yl
896	CH ₃	c-Pr (Me) CH	O	2-NMe ₂ -4-Me-pyrid-5-yl
897	CH ₃	c-Pr (Me) CH	O	2-Cl-4-MeO-6-Me-phenyl
898	CH ₃	c-Pr (Me) CH	O	2-Cl-4,6-Me ₂ -5-F-phenyl
899	CH ₃	c-Pr (Me) CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
900	CH ₃	c-Pr (Me) CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
901	CH ₃	c-Pr (Et) CH	O	2,4,6-Me ₃ -phenyl
902	CH ₃	c-Pr (Et) CH	O	2-Cl-4,6-Me ₂ -phenyl
903	CH ₃	c-Pr (Et) CH	O	2,4-Cl ₂ -6-Me-phenyl
904	CH ₃	c-Pr (Et) CH	O	2,4,6-Cl ₃ -phenyl
905	CH ₃	c-Pr (Et) CH	O	2-Me-4-MeO-phenyl
906	CH ₃	c-Pr (Et) CH	O	2-Cl-4-MeO-phenyl
907	CH ₃	c-Pr (Et) CH	O	2,4,6-Me ₃ -5-F-phenyl
908	CH ₃	c-Pr (Et) CH	O	2,5-Me ₂ -4-MeO-phenyl
909	CH ₃	c-Pr (Et) CH	O	2,4-Me ₂ -6-MeO-phenyl
910	CH ₃	c-Pr (Et) CH	O	2,6-Cl ₂ -4-Me-phenyl
911	CH ₃	c-Pr (Et) CH	O	2,4-Cl ₂ -phenyl
912	CH ₃	c-Pr (Et) CH	O	2-Cl-4-Me-phenyl
913	CH ₃	c-Pr (Et) CH	O	2-Me-4-Cl-phenyl
914	CH ₃	c-Pr (Et) CH	O	2-NMe ₂ -6-Me-pyrid-5-yl
915	CH ₃	c-Pr (Et) CH	O	2-NMe ₂ -4-Me-pyrid-5-yl
916	CH ₃	c-Pr (Et) CH	O	2-Cl-4-MeO-6-Me-phenyl

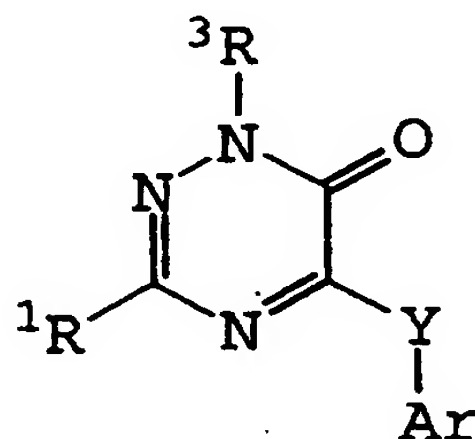
917	CH ₃	c-Pr(Et)CH	O	2-Cl-4,6-Me ₂ -5-F-phenyl
918	CH ₃	c-Pr(Et)CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
919	CH ₃	c-Pr(Et)CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
920	CH ₃	c-Pr(n-Pr)CH	O	2,4,6-Me ₃ -phenyl
921	CH ₃	c-Pr(n-Pr)CH	O	2-Cl-4,6-Me ₂ -phenyl
922	CH ₃	c-Pr(n-Pr)CH	O	2,4-Cl ₂ -6-Me-phenyl
923	CH ₃	c-Pr(n-Pr)CH	O	2,4,6-Cl ₃ -phenyl
924	CH ₃	c-Pr(n-Pr)CH	O	2-Me-4-MeO-phenyl
925	CH ₃	c-Pr(n-Pr)CH	O	2-Cl-4-MeO-phenyl
926	CH ₃	c-Pr(n-Pr)CH	O	2,4,6-Me ₃ -5-F-phenyl
927	CH ₃	c-Pr(n-Pr)CH	O	2,5-Me ₂ -4-MeO-phenyl
928	CH ₃	c-Pr(n-Pr)CH	O	2,4-Me ₂ -6-MeO-phenyl
929	CH ₃	c-Pr(n-Pr)CH	O	2,6-Cl ₂ -4-Me-phenyl
930	CH ₃	c-Pr(n-Pr)CH	O	2,4-Cl ₂ -phenyl
931	CH ₃	c-Pr(n-Pr)CH	O	2-Cl-4-Me-phenyl
932	CH ₃	c-Pr(n-Pr)CH	O	2-Me-4-Cl-phenyl
933	CH ₃	c-Pr(n-Pr)CH	O	2-NMe ₂ -6-Me-pyrid-5-yl
934	CH ₃	c-Pr(n-Pr)CH	O	2-NMe ₂ -4-Me-pyrid-5-yl
935	CH ₃	c-Pr(n-Pr)CH	O	2-Cl-4-MeO-6-Me-phenyl
936	CH ₃	c-Pr(n-Pr)CH	O	2-Cl-4,6-Me ₂ -5-F-phenyl
937	CH ₃	c-Pr(n-Pr)CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
938	CH ₃	c-Pr(n-Pr)CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
939	CH ₃	c-Pr(n-Bu)CH	O	2,4,6-Me ₃ -phenyl
940	CH ₃	c-Pr(n-Bu)CH	O	2-Cl-4,6-Me ₂ -phenyl
941	CH ₃	c-Pr(n-Bu)CH	O	2,4-Cl ₂ -6-Me-phenyl
942	CH ₃	c-Pr(n-Bu)CH	O	2,4,6-Cl ₃ -phenyl
943	CH ₃	c-Pr(n-Bu)CH	O	2-Me-4-MeO-phenyl
944	CH ₃	c-Pr(n-Bu)CH	O	2-Cl-4-MeO-phenyl
945	CH ₃	c-Pr(n-Bu)CH	O	2,4,6-Me ₃ -5-F-phenyl
946	CH ₃	c-Pr(n-Bu)CH	O	2,5-Me ₂ -4-MeO-phenyl
947	CH ₃	c-Pr(n-Bu)CH	O	2,4-Me ₂ -6-MeO-phenyl

948	CH ₃	c-Pr (n-Bu) CH	O	2,6-Cl ₂ -4-Me-phenyl
949	CH ₃	c-Pr (n-Bu) CH	O	2,4-Cl ₂ -phenyl
950	CH ₃	c-Pr (n-Bu) CH	O	2-Cl-4-Me-phenyl
951	CH ₃	c-Pr (n-Bu) CH	O	2-Me-4-Cl-phenyl
952	CH ₃	c-Pr (n-Bu) CH	O	2-NMe ₂ -6-Me-pyrid-5-yl
953	CH ₃	c-Pr (n-Bu) CH	O	2-NMe ₂ -4-Me-pyrid-5-yl
954	CH ₃	c-Pr (n-Bu) CH	O	2-Cl-4-MeO-6-Me-phenyl
955	CH ₃	c-Pr (n-Bu) CH	O	2-Cl-4,6-Me ₂ -5-F-phenyl
956	CH ₃	c-Pr (n-Bu) CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
957	CH ₃	c-Pr (n-Bu) CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
958	CH ₃	c-PrCH ₂ (Et) CH	O	2,4,6-Me ₃ -phenyl
959	CH ₃	c-PrCH ₂ (Et) CH	O	2-Cl-4,6-Me ₂ -phenyl
960	CH ₃	c-PrCH ₂ (Et) CH	O	2,4-Cl ₂ -6-Me-phenyl
961	CH ₃	c-PrCH ₂ (Et) CH	O	2,4,6-Cl ₃ -phenyl
962	CH ₃	c-PrCH ₂ (Et) CH	O	2-Me-4-MeO-phenyl
963	CH ₃	c-PrCH ₂ (Et) CH	O	2-Cl-4-MeO-phenyl
964	CH ₃	c-PrCH ₂ (Et) CH	O	2,4,6-Me ₃ -5-F-phenyl
965	CH ₃	c-PrCH ₂ (Et) CH	O	2,5-Me ₂ -4-MeO-phenyl
966	CH ₃	c-PrCH ₂ (Et) CH	O	2,4-Me ₂ -6-MeO-phenyl
967	CH ₃	c-PrCH ₂ (Et) CH	O	2,6-Cl ₂ -4-Me-phenyl
968	CH ₃	c-PrCH ₂ (Et) CH	O	2,4-Cl ₂ -phenyl
969	CH ₃	c-PrCH ₂ (Et) CH	O	2-Cl-4-Me-phenyl
970	CH ₃	c-PrCH ₂ (Et) CH	O	2-Me-4-Cl-phenyl
971	CH ₃	c-PrCH ₂ (Et) CH	O	2-NMe ₂ -6-Me-pyrid-5-yl
972	CH ₃	c-PrCH ₂ (Et) CH	O	2-NMe ₂ -4-Me-pyrid-5-yl
973	CH ₃	c-PrCH ₂ (Et) CH	O	2-Cl-4-MeO-6-Me-phenyl
974	CH ₃	c-PrCH ₂ (Et) CH	O	2-Cl-4,6-Me ₂ -5-F-phenyl
975	CH ₃	c-PrCH ₂ (Et) CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
976	CH ₃	c-PrCH ₂ (Et) CH	O	6-Me-2,3-dihydro-benzofuran-5-yl
977	CH ₃	Et ₂ CH	O	2,4-Cl ₂ -6-Me-phenyl
978	CH ₃	Et ₂ CH	O	2,4,6-Cl ₃ -phenyl

979	CH ₃	Et ₂ CH	O	2-Me-4-MeO-phenyl
980	CH ₃	Et ₂ CH	O	2-Cl-4-MeO-phenyl
981	CH ₃	Et ₂ CH	O	2,4,6-Me ₃ -5-F-phenyl
982	CH ₃	Et ₂ CH	O	2,5-Me ₂ -4-MeO-phenyl
983	CH ₃	Et ₂ CH	O	2,4-Me ₂ -6-MeO-phenyl
984	CH ₃	Et ₂ CH	O	2,6-Cl ₂ -4-Me-phenyl
985	CH ₃	Et ₂ CH	O	2,4-Cl ₂ -phenyl
986	CH ₃	Et ₂ CH	O	2-Cl-4-Me-phenyl
987	CH ₃	Et ₂ CH	O	2-Me-4-Cl-phenyl
988	CH ₃	Et ₂ CH	O	2-NMe ₂ -6-Me-pyrid-5-yl
989	CH ₃	Et ₂ CH	O	2-NMe ₂ -4-Me-pyrid-5-yl
990	CH ₃	Et ₂ CH	O	2-Cl-4,6-Me ₂ -5-F-phenyl
991	CH ₃	Et ₂ CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl
992	CH ₃	Et ₂ CH	O	6-Me-2,3-dihydro-benzofuran-5-yl

Additional compounds, wherein Y = oxygen that can be synthesized using synthetic Scheme 6 or Scheme 7 are listed in Table 4

5

Table 4

Ex. No.	R ¹	R ³	Y	Ar	mp
1000	CH ₃	Et ₂ CH	O	2,4,6-Me ₃ -phenyl	
1001	CH ₃	Et ₂ CH	O	2-Cl-4,6-Me ₂ -phenyl	
1002	CH ₃	Et ₂ CH	O	2,4-Cl ₂ -6-Me-phenyl	
1003	CH ₃	Et ₂ CH	O	2,4,6-Cl ₃ -phenyl	
1004	CH ₃	Et ₂ CH	O	2-Me-4-MeO-phenyl	
1005	CH ₃	Et ₂ CH	O	2-Cl-4-MeO-phenyl	
1006	CH ₃	Et ₂ CH	O	2,4,6-Me ₃ -5-F-phenyl	
1007	CH ₃	Et ₂ CH	O	2,5-Me ₂ -4-MeO-phenyl	
1008	CH ₃	Et ₂ CH	O	2,4-Me ₂ -6-MeO-phenyl	
1009	CH ₃	Et ₂ CH	O	2,6-Cl ₂ -4-Me-phenyl	
1010	CH ₃	Et ₂ CH	O	2,4-Cl ₂ -phenyl	
1011	CH ₃	Et ₂ CH	O	2-Cl-4-Me-phenyl	
1012	CH ₃	Et ₂ CH	O	2-Me-4-Cl-phenyl	
1013	CH ₃	Et ₂ CH	O	2-NMe ₂ -6-Me-pyrid-5-yl	
1014	CH ₃	Et ₂ CH	O	2-NMe ₂ -4-Me-pyrid-5-yl	
1015	CH ₃	Et ₂ CH	O	2-Cl-4-MeO-6-Me-phenyl	
1016	CH ₃	Et ₂ CH	O	2-Cl-4,6-Me ₂ -5-F-phenyl	
1017	CH ₃	Et ₂ CH	O	6-Cl-2,3-dihydro-benzofuran-5-yl	
1018	CH ₃	Et ₂ CH	O	6-Me-2,3-dihydro-benzofuran-5-yl	

Utility5 CRF-R1 Receptor Binding Assay for the Evaluation of
Biological Activity

10 The following is a description of the isolation
of cell membranes containing cloned human CRF-R1 receptors
for use in the standard binding assay as well as a
description of the assay itself.

Messenger RNA was isolated from human hippocampus.
The mRNA was reverse transcribed using oligo (dt) 12-18 and
the coding region was amplified by PCR from start to stop
codons. The resulting PCR fragment was cloned into the
15 EcoRV site of pGEMV, from whence the insert was reclaimed
using XhoI + XbaI and cloned into the XhoI + XbaI sites of
vector pm3ar (which contains a CMV promoter, the SV40 't'
splice and early poly A signals, an Epstein-Barr viral
origin of replication, and a hygromycin selectable marker).
20 The resulting expression vector, called phchCRFR was
transfected in 293EBNA cells and cells retaining the
episome were selected in the presence of 400 mM hygromycin.
Cells surviving 4 weeks of selection in hygromycin were
pooled, adapted to growth in suspension and used to
25 generate membranes for the binding assay described below.
Individual aliquots containing approximately 1×10^8 of the
suspended cells were then centrifuged to form a pellet and
frozen.

For the binding assay a frozen pellet described above
30 containing 293EBNA cells transfected with hCRFR1 receptors
is homogenized in 10 ml of ice cold tissue buffer (50 mM
HEPES buffer pH 7.0, containing 10 mM $MgCl_2$, 2 mM EGTA, 1
mg/l aprotinin, 1 mg/ml leupeptin and 1 mg/ml pepstatin).
The homogenate is centrifuged at 40,000 x g for 12 min and
35 the resulting pellet rehomogenized in 10 ml of tissue
buffer. After another centrifugation at 40,000 x g for 12

min, the pellet is resuspended to a protein concentration of 360 mg/ml to be used in the assay.

Binding assays are performed in 96 well plates; each well having a 300 ml capacity. To each well is added 50 ml of test drug dilutions (final concentration of drugs range from 10^{-10} - 10^{-5} M), 100 ml of ^{125}I -ovine-CRF (^{125}I -o-CRF) (final concentration 150 pM) and 150 ml of the cell homogenate described above. Plates are then allowed to incubate at room temperature for 2 hours before filtering the incubate over GF/F filters (presoaked with 0.3% polyethyleneimine) using an appropriate cell harvester. Filters are rinsed 2 times with ice cold assay buffer before removing individual filters and assessing them for radioactivity on a gamma counter.

Curves of the inhibition of ^{125}I -o-CRF binding to cell membranes at various dilutions of test drug are analyzed by the iterative curve fitting program LIGAND [P.J. Munson and D. Rodbard, *Anal. Biochem.* 107:220 (1980)], which provides K_i values for inhibition which are then used to assess biological activity.

A compound is considered to be active if it has a K_i value of less than about 10000 nM for the inhibition of CRF. Compounds with a K_i less than 100 nM for the inhibition of CRF are desirable. A number of compounds of the invention have been made and tested in the above assay and shown to have K_i values less than 100 nM thus confirming the utility of the invention.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity was performed as described by G. Battaglia et al. *Synapse* 1:572 (1987). Briefly, assays were carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM MgCl_2 , 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides

(concentration range 10^{-9} to 10^{-6} m) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions were initiated by the addition of 1 mM ATP/ 32 P]ATP (approximately 2-4 mCi/tube) and terminated by the addition
5 of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 μ l of [3 H]cAMP (approximately 40,000 dpm) was added to each tube prior to separation. The separation of [32 P]cAMP from [32 P]ATP was performed by sequential elution over
10 Dowex and alumina columns. Recovery was consistently greater than 80%.

A compound of this invention was tested in this assay and found to be active; $IC_{50} < 10000$ nM.

15 In vivo Biological Assay

The in vivo activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic Startle Assay, the
20 Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn *Brain Research Reviews* 15:71 (1990)

Compounds may be tested in any species of rodent or
25 small mammal. Disclosure of the assays herein is not intended to limit the enablement of the invention.

Compounds of this invention have utility in the treatment of imbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from
30 depression, affective disorders, and/or anxiety.

Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any
35 conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be

administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

- 5 The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent
- 10 treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10
- 15 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

- Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of
- 20 active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

- The active ingredient can be administered orally is
- 25 solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

- 30 Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be
- 35 manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to

mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement was pumped

into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

5

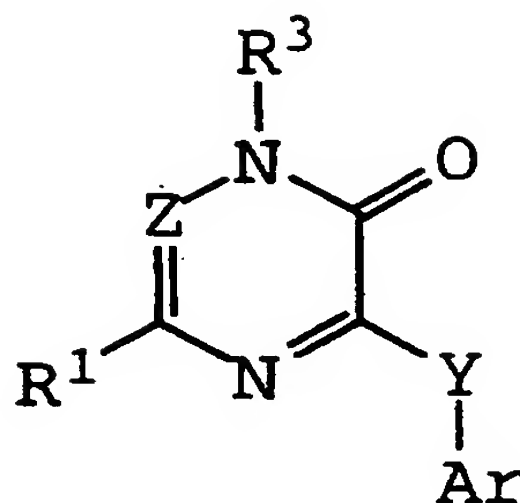
Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline
10 cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of this invention may also be used as
15 reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

Claims:

1. A composition of matter comprising compound of Formula I



(I)

or a pharmaceutically acceptable salt form thereof, wherein Z is CR² or N;

when Z is CR²:

Y is NR⁴, O or S(O)_n;

Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, indolinyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, benzothiazolyl, indazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 4 R⁵ groups; wherein Ar is attached to Y through an unsaturated carbon;

R¹ is H, halo, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CONR⁶R⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, or -NR⁶R⁷,

wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷,

- CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷,
 -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl;
 R² is H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl,
 C₃-C₆ cycloalkyl, halo, -CN, C₁-C₄ haloalkyl, -NR⁹R¹⁰,
 5 -NR⁹COR¹⁰, -NR⁹CO₂R¹⁰, -OR¹¹, -SH or -S(O)_nR¹²;
 R³ is C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl,
 heterocyclyl, -CN, -OR⁷, -S(O)₂R¹³, -COR⁷, -CO₂R⁷,
 -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -CONR⁶R⁷, -NR⁸CO₂R⁷,
 10 or -NR⁶R⁷,
 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl
 or C₃-C₈ cycloalkyl is each substituted with 0 to 3
 substituents independently selected at each
 occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
 15 C₁-C₄ haloalkyl, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷,
 -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷,
 -CONR⁶R⁷, aryl and heterocyclyl,
 with the proviso that when R³ is aryl, Ar is not
 imidazolyl;
 20 R⁴ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl,
 wherein C₂-C₆ alkenyl or C₂-C₆ alkynyl is optionally
 substituted with C₁-C₄ alkyl or C₃-C₆ cycloalkyl and
 wherein C₁-C₆ alkyl is optionally substituted with
 C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, -OR⁷,
 25 -S(O)_nR¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;
 R⁵ is independently selected at each occurrence from
 C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆
 cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl,
 heterocyclyl, -NO₂, halo, -CN, C₁-C₄ haloalkyl,
 30 -NR⁶R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷, -OR⁷, -COR⁷, -CO₂R⁷,
 -CONR⁶R⁷, -CON(OR⁹)R⁷, -SH, and -S(O)_nR¹³,
 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl,
 C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl are
 substituted with 0 to 3 substituents independently
 35 selected at each occurrence from C₁-C₄ alkyl, -NO₂,
 halo, -CN, -OR⁷, -COR⁷, -CO₂R⁷, -CONR⁶R⁷, -NR⁶R⁷,
 -NR⁸COR⁷, -NR⁸CO₂R⁷ and -S(O)_nR¹³;

R⁶ and R⁷ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl, heterocyclyl(C₁-C₄ alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or -NR⁶R⁷ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

wherein C₁-C₄ alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C₁-C₄ alkoxy groups;

R⁸ is independently at each occurrence H or C₁-C₄ alkyl;

R⁹ and R¹⁰ are independently at each occurrence selected from H, C₁-C₄ alkyl and C₃-C₆ cycloalkyl;

R¹¹ is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;

R¹² is C₁-C₄ alkyl, C₁-C₄ haloalkyl or -NR⁶R⁷;

R¹³ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR⁶R⁷, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-;

R¹⁴ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR¹⁵R¹⁶;

R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl; or -NR¹⁵R¹⁶ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl, biphenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR¹⁵, -SH, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -OC(O)R¹⁴, -NO₂, -NR⁸COR¹⁵, -N(COR¹⁵)₂, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵, -NR¹⁵R¹⁶ and -CONR¹⁵R¹⁶;

heterocyclyl is 5- to 10- membered heterocyclic ring which may be saturated, partially unsaturated or aromatic, and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S, wherein the heterocyclic ring is substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR¹⁵, -SH, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -OC(O)R¹⁴, -NR⁸COR¹⁵, -N(COR¹⁵)₂, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵, -NR¹⁵R¹⁶, and -CONR¹⁵R¹⁶; and n is independently at each occurrence 0, 1 or 2;

and wherein, when Z is N:
 Y is NR⁴, O or S(O)_n;
 Ar, R¹, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, aryl, heterocyclyl, heterocyclyl and n are as defined above, but
 R³ is C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -S(O)₂R¹³, -CO₂R⁷, -COR⁷ or -CONR⁶R⁷,
 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl,
 with the proviso that when R³ is aryl, Ar is not imidazolyl.

2. A composition of matter comprising a compound of Claim 1 wherein:

Z is CR²;
 Y is NR⁴, O, S(O)_n;

- Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, indolinyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, benzothiazolyl, indazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 4 R⁵ groups; wherein Ar is attached to Y through an unsaturated carbon;
- 10 R¹ is H, halo, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CONR⁶R⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, or -NR⁶R⁷,
- 15 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl;
- 20 R² is H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, halo, -CN, C₁-C₄ haloalkyl, -NR⁹R¹⁰, -NR⁹COR¹⁰, -NR⁹CO₂R¹⁰, -OR¹¹, -SH or -S(O)_nR¹²;
- 25 R³ is C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -OR⁷, -S(O)₂R¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -CONR⁶R⁷, -NR⁸CO₂R⁷, or -NR⁶R⁷,
- 30 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl,
- 35

with the proviso that when R^3 is aryl, Ar is not imidazolyl;

R^4 is H, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl, wherein C₂-C₆ alkenyl or C₂-C₆ alkynyl is optionally substituted with C₁-C₄ alkyl or C₃-C₆ cycloalkyl and wherein C₁-C₆ alkyl is optionally substituted with C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, -OR⁷, -S(O)_nR¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;

R^5 is independently selected at each occurrence from C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, heterocyclyl, -NO₂, halo, -CN, C₁-C₄ haloalkyl, -NR⁶R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷, -OR⁷, -COR⁷, -CO₂R⁷, -CONR⁶R⁷, -CON(OR⁹)R⁷, -SH, and -S(O)_nR¹³, wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN, -OR⁷, -COR⁷, -CO₂R⁷, -CONR⁶R⁷, -NR⁶R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷ and -S(O)_nR¹³;

R^6 and R^7 are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl, heterocyclyl(C₁-C₄ alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or NR⁶R⁷ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C₁-C₄ alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C₁-C₄ alkoxy groups;

R^8 is independently at each occurrence H or C₁-C₄ alkyl;

R^9 and R^{10} are independently at each occurrence selected from H, C₁-C₄ alkyl and C₃-C₆ cycloalkyl;

R^{11} is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;

- R^{12} is C₁-C₄ alkyl, C₁-C₄ haloalkyl or -NR⁶R⁷;
- R^{13} is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR⁶R⁷, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-;
- R^{14} is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR¹⁵R¹⁶;
- R^{15} and R^{16} are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl; or -NR¹⁵R¹⁶ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;
- aryl is phenyl, biphenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR¹⁵, -SH, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -OC(O)R¹⁴, -NO₂, -NR⁸COR¹⁵, -N(COR¹⁵)₂, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵, -NR¹⁵R¹⁶ and -CONR¹⁵R¹⁶;
- heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR¹⁵, -SH, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -OC(O)R¹⁴, -NO₂, -NR⁸COR¹⁵, -N(COR¹⁵)₂, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵, -NR¹⁵R¹⁶ and -CONR¹⁵R¹⁶; and
- n is independently at each occurrence 0, 1 or 2.

3. A composition of matter comprising a compound of Claim 2 wherein:

- Z is CR²;
- Y is NR⁴ or O;

- Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵ groups;
- R¹ is H, halo, C₁-C₄ alkyl, cyclopropyl, C₁-C₄ haloalkyl, -CN, -NR⁶R⁷, -CONR⁶R⁷, -OR⁷, -COR⁷, -CO₂R⁷ or
 5 -S(O)_nR¹³,
 wherein C₁-C₄ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, C₃-C₆ cycloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷,
 10 -NR⁸CO₂R⁷, -NR⁶R⁷ and aryl;
- R² is H, C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl;
- R³ is C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -OR⁷, -S(O)₂R¹³, -COR⁷, -CO₂R⁷,
 15 -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -CONR⁶R⁷, -NR⁸CO₂R⁷, or -NR⁶R⁷,
 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -CO₂R⁷, -NR⁸COR⁷, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, aryl and heterocyclyl;
- 20 R⁴ is H, C₁-C₆ alkyl or C₂-C₆ alkenyl, wherein C₁-C₆ alkyl is optionally substituted with C₁-C₄ alkyl, C₁-C₄ haloalkyl, -OR⁷, -S(O)_nR¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;
- R⁵ is independently selected at each occurrence from C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₄-C₈ cycloalkylalkyl, aryl, heterocyclyl, C₁-C₄ haloalkyl, halo, -CN, -NO₂, -NR⁶R⁷, -COR⁷, -OR⁷, -CONR⁶R⁷, -CON(OR⁹)R⁷, CO₂R⁷ and -S(O)_nR¹³,
 30 wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl and C₄-C₈ cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, -NO₂,
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halo, -CN, -NR⁶R⁷, COR⁷, -OR⁷, -CONR⁶R⁷, CO₂R⁷ and -S(O)_nR¹³;

- R⁶ and R⁷ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl, heterocyclyl(C₁-C₄ alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or -NR⁶R⁷ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C₁-C₄ alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C₁-C₄ alkoxy groups;
- R⁸ is independently at each occurrence H or C₁-C₄ alkyl; R⁹ and R¹⁰ are independently at each occurrence selected from H, C₁-C₄ alkyl and C₃-C₆ cycloalkyl; R¹¹ is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;
- R¹² is C₁-C₄ alkyl, C₁-C₄ haloalkyl or -NR⁶R⁷; R¹³ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR⁶R⁷, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-;
- R¹⁴ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR¹⁵R¹⁶; R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl; or -NR¹⁵R¹⁶ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine; aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵ and -NR¹⁵R¹⁶;

heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵, and -NR¹⁵R¹⁶; and
n is independently at each occurrence 0, 1 or 2.

4. A composition of matter comprising compound of Claim 3 wherein:

Z is CR²;

Y is NR⁴;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵ groups;

R¹ is H, halo, C₁-C₄ alkyl, cyclopropyl, C₁-C₃ haloalkyl, -CN, -NR⁶R⁷, -CONR⁶R⁷, -COR⁷, -CO₂R⁷, -OR⁷ or -S(O)_nR¹³ wherein C₁-C₄ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₃-C₄ cycloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁶R⁷;

R² is H;

R³ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl or aryl, wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or C₃-C₆ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -CO₂R⁷, -NR⁸COR⁷, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷ and aryl;

R⁴ is H, allyl, or C₁-C₄ alkyl, wherein C₁-C₄ alkyl is optionally substituted with C₁-C₄ alkyl, -OR⁷, -S(O)₂R¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;

R⁵ is independently selected at each occurrence from C₁-C₆ alkyl, aryl, heterocyclyl, C₁-C₄ haloalkyl, halo, -CN, -NO₂, -NR⁶R⁷, -COR⁷, -OR⁷, -CONR⁶R⁷,

-CON(OR⁹)R⁷, -CO₂R⁷ and -S(O)_nR¹³, wherein C₁-C₆ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN, -NR⁶R⁷, COR⁷, -OR⁷, -CONR⁶R⁷, CO₂R⁷ and -S(O)_nR¹³;
5 R⁶ and R⁷ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₂-C₈ alkoxyalkyl;
wherein C₁-C₄ alkyl, may be substituted with 0 to 2
10 substituents independently selected at each occurrence from -OH or C₁-C₄ alkoxy groups;
R⁸, R⁹ and R¹⁰ are independently at each occurrence H or C₁-C₄ alkyl;
R¹² and R¹³ are independently at each occurrence C₁-C₄
15 alkyl or -NR⁶R⁷;
R¹⁴ is C₁-C₄ alkyl or -NR¹⁵R¹⁶;
R¹⁵ and R¹⁶ are independently at each occurrence H, C₁-C₄ alkyl or C₂-C₈ alkoxyalkyl;
aryl is phenyl substituted with 0 to 3 substituents
20 independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂ and -NR¹⁵R¹⁶; and
n is independently at each occurrence 0, 1 or 2.

25 5. A composition of matter comprising compound of Claim 4 wherein:

Z is CR²;
Y is NR⁴;
30 Ar is phenyl or pyridyl, each substituted with 2 to 4 R⁵ groups;
R¹ is H, Cl, Br, methyl, ethyl, cyclopropyl, or -CN,
R² is H;
R³ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,
35 C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl or aryl,
wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or C₃-C₆ cycloalkyl is each substituted with 0 to 3

- substituents independently selected at each occurrence from C₁-C₄ alkyl, C₃-C₆ cycloalkyl, -CF₃, halo, -CN, -OR⁷, and aryl;
- 5 R⁴ is H, methyl, ethyl, i-propyl, n-propyl, n-butyl, i-butyl, s-butyl, n-butyl, or allyl;
- R⁵ is independently selected at each occurrence from methyl, ethyl, i-propyl, n-propyl, aryl, -CF₃, halo, -CN, -N(CH₃)₂, -C(=O)CH₃, -OCH₃, -OCH₂CH₃, -OCF₃, and -S(O)₂CH₃;
- 10 R¹⁴ is C₁-C₄ alkyl or -NR¹⁵R¹⁶;
- R¹⁵ and R¹⁶ are independently at each occurrence H, C₁-C₄ alkyl or C₂-C₈ alkoxyalkyl;
- aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from
- 15 C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂ and -NR¹⁵R¹⁶; and
- n is independently at each occurrence 0, 1 or 2.

6. A composition of matter comprising compounds of
- 20 Claim 4 which are:

3-[(2,4-Dibromophenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

- 25 3-[[2-Bromo-4-(1-methylethyl)phenyl]amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[(2,4-Dibromophenyl)ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

- 30 3-[[2-Bromo-4-(1-methylethyl)phenyl]ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

- 35 3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)ethylamino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

5 (+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2-Bromo-4,6-dimethoxyphenyl)amino]-5-chloro-1-(1-ethylpropyl)-2(1H)-pyrazinone;

10 3-[(2-Cyano-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

15 (+/-)-3-[(2-Bromo-4,6-dimethoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2-Chloro-4,6-dimethoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

20 (+/-)-3-[(4,6-Dimethyl-2-iodophenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2-Cyano-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

25 (+/-)-3-[(2-Bromo-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

30 (+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

35 (+/-)-3-[(2-Acetyl-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4,6-Dimethyl-2-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

5 (+/-)-3-[(4,6-Dimethyl-2-methylsulfonylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Chloro-2-iodo-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

10 3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-phenyl-2(1H)-pyrazinone;

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(+/-)-3-[(2,4-Dibromophenyl)amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

20 (+/-)-3-[[2-Bromo-4-(1-methylethyl)phenyl]amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

25 3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,4-Dichloro-6-methylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

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3-[(2,4-Dichloro-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

35 3-[(2,4-Dibromo-6-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

- (+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 5 (+/-)-3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 3-[(2,4,6-Trimethylphenyl)amino]-5-chloro-1-[1-(2-methoxyethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 10 (+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;
- (+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 15 (+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- (+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 20 (+/-)-3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 25 (+/-)-3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;
- 3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 30 3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;
- 35 3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

5 (+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

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(+/-)-3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

15 (+/-)-3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-chloro-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

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3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

25 3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[[2,4-Dimethyl-6-(methoxymethyl)phenyl]amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

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(+/-)-3-[(2,4-Dimethyl-6-methoxyphenyl)amino]-5-chloro-1-(2-methoxy-1-methylethyl)-2(1H)-pyrazinone;

35 (+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-(2-methoxy-1-methylethyl)-2(1H)-pyrazinone;

(+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-[1-(ethoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-chloro-1-(2-ethoxy-1-methylethyl)-2(1H)-pyrazinone; and

(+/-)-3-[(4-Bromo-2,6-difluorophenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

10 (+/-)-3-[(2-Bromo-4,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-thiomethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,4-Dimethyl-6-methylsulfonylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

20 (+/-)-3-[(2,6-Dimethyl-4-(N,N-dimethylamino)phenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

25 (+/-)-3-[(2,4-Dichloro-6-methylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(4-Chloro-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

30 (+/-)-3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

35 (+/-)-3-[(2,6-Dimethyl-4-methoxyphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

(+/-)-3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

5 (+/-)-3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-3-methoxypropyl]-2(1H)-pyrazinone;

3-[(4-Bromo-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

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3-[(4-Acetyl-2,6-dimethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

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3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

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3-[(2,6-Dimethyl-4-(N,N-dimethylamino)phenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

25 3-[(4,6-Dimethyl-2-(N,N-dimethylamino)phenyl)amino]-5-methyl-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

(+/-)3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

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(+/-)3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

35 (+/-)3-[(2-Chloro-4,6-dimethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

(+/-) 3-[(4-Bromo-6-methoxy-2-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)propyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-thiomethylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

3-[(2,6-Dimethyl-4-methylsulfonylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone;

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3-[(4-Bromo-6-methoxy-2-methylphenyl)amino]-5-chloro-1-[1-(methoxymethyl)-2-methoxyethyl]-2(1H)-pyrazinone; and

3-[(2,4,6-Trimethylphenyl)amino]-5-methyl-1-(1-ethylpropyl)-2(1H)-pyrazinone.

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7. A composition of matter comprising compound of Claim 2 wherein:

20 Z is CR²;

Y is NR⁴ or O;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵ groups;

R¹ is H, halo, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CONR⁶R⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, or -NR⁶R⁷,

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wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl;

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R² is H, C₁-C₄ alkyl, halo, C₁-C₄ haloalkyl;

- R^3 is C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl and -NR⁶R⁷,
wherein C₁-C₄ alkyl is substituted with 0 to 3
substituents independently selected at each
occurrence from C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄
haloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷,
-NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷
and -CONR⁶R⁷;
- R^4 is H, C₁-C₆ alkyl or C₂-C₆ alkenyl, wherein C₁-C₆ alkyl
is optionally substituted with C₁-C₄ alkyl, C₁-C₄
haloalkyl, -OR⁷, -S(O)_nR¹², -CO₂R⁷, -NR⁶R⁷ or
-NR⁹COR¹⁰;
- R^5 is independently selected at each occurrence from
C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆
cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl,
heterocyclyl, -NO₂, halo, -CN, C₁-C₄ haloalkyl,
-NR⁶R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷, -OR⁷, -COR⁷, -CO₂R⁷,
-CONR⁶R⁷, -CON(OR⁹)R⁷ and -S(O)_nR¹³, wherein
C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆
cycloalkyl and C₄-C₁₂ cycloalkylalkyl are substituted
with 0 to 3 substituents independently selected at
each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN,
-OR⁷, -COR⁷, -CO₂R⁷, -CONR⁶R⁷, -NR⁶R⁷, -NR⁸COR⁷,
-NR⁸CO₂R⁷ and -S(O)_nR¹³;
- R^6 and R^7 are independently selected at each occurrence
from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈
alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-
C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-,
heterocyclyl, heterocyclyl (C₁-C₄ alkyl)-,
morpholinoethyl, morpholinopropyl and
morpholinobutyl; or -NR⁶R⁷ taken together as a whole
is piperidine, pyrrolidine, piperazine, N-methyl-
piperazine, morpholine or thiomorpholine;
wherein C₁-C₄ alkyl, may be substituted with 0 to 2
substituents independently selected at each
occurrence from -OH or C₁-C₄ alkoxy groups;
- R^8 is independently at each occurrence H or C₁-C₄ alkyl;

- R^9 and R^{10} are independently at each occurrence selected from H, C₁-C₄ alkyl and C₃-C₆ cycloalkyl;
- R^{11} is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;
- 5 R^{12} is C₁-C₄ alkyl, C₁-C₄ haloalkyl or -NR⁶R⁷;
- R^{13} is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR⁶R⁷, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-;
- 10 R^{14} is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR¹⁵R¹⁶;
- R^{15} and R^{16} are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl and C₄-
- 15 C₁₂ cycloalkylalkyl; or -NR¹⁵R¹⁶ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;
- aryl is phenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each
- 20 occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵ and -NR¹⁵R¹⁶;
- heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl,
- 25 isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵, and -NR¹⁵R¹⁶; and
- 30 n is independently at each occurrence 0, 1 or 2.

8. A composition of matter comprising compound of Claim 7 wherein:

- 35 Z is CR²;
- Y is NR⁴;

- Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵ groups;
- R¹ is H, halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CONR⁶R⁷, -CO₂R⁷ or -NR⁶R⁷,
 wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or C₃-C₆ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl;
- R² is H;
- R³ is C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl and -NR⁶R⁷,
 wherein C₁-C₄ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷ and -CONR⁶R⁷;
- R⁴ is H, allyl, or C₁-C₄ alkyl, wherein C₁-C₄ alkyl is optionally substituted with C₁-C₄ alkyl, -OR⁷, -S(O)₂R¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;
- R⁵ is independently selected at each occurrence from C₁-C₆ alkyl, aryl, heterocyclyl, C₁-C₄ haloalkyl, halo, -CN, -NO₂, -NR⁶R⁷, -COR⁷, -OR⁷, -CONR⁶R⁷, -CON(OR⁹)R⁷, -CO₂R⁷ and -S(O)_nR¹³, wherein C₁-C₆ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN, -NR⁶R⁷, COR⁷, -OR⁷, -CONR⁶R⁷, CO₂R⁷ and -S(O)_nR¹³;
- R⁶ and R⁷ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₂-C₈ alkoxyalkyl;

wherein C₁-C₄ alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C₁-C₄ alkoxy groups;

R⁸, R⁹ and R¹⁰ are independently at each occurrence H or C₁-C₄ alkyl;

R¹² and R¹³ are independently at each occurrence C₁-C₄ alkyl or -NR⁶R⁷;

R¹⁴ is C₁-C₄ alkyl or -NR¹⁵R¹⁶;

R¹⁵ and R¹⁶ are independently at each occurrence H, C₁-C₄ alkyl or C₂-C₈ alkoxyalkyl;

aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂ and -NR¹⁵R¹⁶; and

n is independently at each occurrence 0, 1 or 2.

9. A composition of matter comprising compound of Claim 1 wherein:

Z is N;

Y is NR⁴, O or S(O)_n;

Ar is phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, indolinyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, benzothiazolyl, indazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 4 R⁵ groups; wherein Ar is attached to Y through an unsaturated carbon;

R¹ is H, halo, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CONR⁶R⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, or -NR⁶R⁷,

wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3

- substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl;
- 5 R³ is C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -S(O)₂R¹³, -CO₂R⁷, -COR⁷ or -CONR⁶R⁷,
- 10 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷,
- 15 -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl, with the proviso that when R³ is aryl, Ar is not imidazolyl;
- R⁴ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl,
- 20 wherein C₂-C₆ alkenyl or C₂-C₆ alkynyl is optionally substituted with C₁-C₄ alkyl or C₃-C₆ cycloalkyl and wherein C₁-C₆ alkyl is optionally substituted with C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, -OR⁷, -S(O)_nR¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;
- 25 R⁵ is independently selected at each occurrence from C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, heterocyclyl, halo, C₁-C₄ haloalkyl, -CN, -NO₂, -NR⁶R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷, -OR⁷, -COR⁷, -CO₂R⁷,
- 30 -CONR⁶R⁷, -CON(OR⁹)R⁷ and -S(O)_nR¹³, wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN,
- 35 -OR⁷, -COR⁷, -CO₂R⁷, -CONR⁶R⁷, -NR⁶R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷, -SH, and -S(O)_nR¹³;

R⁶ and R⁷ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl, heterocyclyl(C₁-C₄ alkyl)-, morpholinoethyl, morpholinopropyl and morpholinobutyl; or NR⁶R⁷ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C₁-C₄ alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C₁-C₄ alkoxy groups;

R⁸ is independently at each occurrence H or C₁-C₄ alkyl; R⁹ and R¹⁰ are independently at each occurrence selected from H, C₁-C₄ alkyl and C₃-C₆ cycloalkyl;

R¹¹ is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;

R¹² is C₁-C₄ alkyl, C₁-C₄ haloalkyl or -NR⁶R⁷;

R¹³ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR⁶R⁷, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-;

R¹⁴ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR¹⁵R¹⁶;

R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl; or -NR¹⁵R¹⁶ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;

aryl is phenyl, biphenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR¹⁵, -SH, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -OC(O)R¹⁴, -NO₂, -NR⁸COR¹⁵, -N(COR¹⁵)₂, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵, -NR¹⁵R¹⁶ and -CONR¹⁵R¹⁶;

heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR¹⁵, -SH, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -OC(O)R¹⁴, -NO₂, -NR⁸COR¹⁵, -N(COR¹⁵)₂, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵, -NR¹⁵R¹⁶ and -CONR¹⁵R¹⁶, and

n is independently at each occurrence 0, 1 or 2.

10. A composition of matter comprising compound of Claim 9 wherein:

Z is N;

Y is NR⁴ or O;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵ groups;

R¹ is H, halo, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, aryl, -CN, C₁-C₄ haloalkyl, -NR⁶R⁷, -CONR⁶R⁷, -OR⁷, -COR⁷, -CO₂R⁷ or -S(O)_nR¹³,

wherein C₁-C₄ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₃ alkyl, C₃-C₆ cycloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷, -NR⁶R⁷ and aryl;

R³ is C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -S(O)₂R¹³, -COR⁷, -CO₂R⁷ or -CONR⁶R⁷,

wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -CO₂R⁷,

-NR⁸COR⁷, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, aryl and heterocyclyl;

5 R⁴ is H, C₁-C₆ alkyl or C₂-C₆ alkenyl, wherein C₁-C₆ alkyl is optionally substituted with C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, -OR⁷, -S(O)_nR¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;

10 R⁵ is independently selected at each occurrence from C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₄-C₈ cycloalkylalkyl, aryl, heterocyclyl, C₁-C₄ haloalkyl, halo, -CN, -NO₂, -NR⁶R⁷, -COR⁷, -OR⁷, -CONR⁶R⁷, -CON(OR⁹)R⁷, CO₂R⁷ and -S(O)_nR¹³,

15 wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl and C₄-C₈ cycloalkylalkyl are substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN, -NR⁶R⁷, COR⁷, -OR⁷, -CONR⁶R⁷, CO₂R⁷ and -S(O)_nR¹³;

20 R⁶ and R⁷ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl, heterocyclyl(C₁-C₄ alkyl)-, morpholinoethyl, morpholinopropyl and
25 morpholinobutyl; or -NR⁶R⁷ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C₁-C₄ alkyl, may be substituted with 0 to 2 substituents independently selected at each
30 occurrence from -OH or C₁-C₄ alkoxy groups;

R⁸ is independently at each occurrence H or C₁-C₄ alkyl;

R⁹ and R¹⁰ are independently at each occurrence selected from H, C₁-C₄ alkyl and C₃-C₆ cycloalkyl;

35 R¹¹ is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl;

R¹² is C₁-C₄ alkyl, C₁-C₄ haloalkyl or -NR⁶R⁷;

- R^{13} is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR⁶R⁷, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl or heterocyclyl(C₁-C₄ alkyl)-;
- 5 R^{14} is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR¹⁵R¹⁶;
 R^{15} and R^{16} are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl and C₄-
10 C₁₂ cycloalkylalkyl; or -NR¹⁵R¹⁶ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;
aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from
15 C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵ and -NR¹⁵R¹⁶;
heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl,
20 isoxazolyl or pyrazolyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵, -NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵, and -NR¹⁵R¹⁶; and
25 n is independently at each occurrence 0, 1 or 2.

11. A composition of matter comprising compound of Claim 10 wherein:

- 30 Z is N;
Y is NR⁴;
Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵ groups;
 R^1 is H, halo, C₁-C₄ alkyl, C₁-C₃ haloalkyl, cyclopropyl,
35 -CN, -NR⁶R⁷, -CONR⁶R⁷, -COR⁷, -CO₂R⁷, -OR⁷ or -S(O)_nR¹³ wherein C₁-C₄ alkyl is substituted with 0 to 3 substituents independently selected at each

- occurrence from C₃-C₄ cycloalkyl, halo, -CN, -OR⁷,
-S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁶R⁷;
- 5 R³ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,
C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl or aryl,
wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or
C₃-C₆ cycloalkyl is each substituted with 0 to 3
substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl,
C₁-C₄ haloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -CO₂R⁷,
10 -NR⁸COR⁷, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷ and aryl;
- R⁴ is H, allyl, or C₁-C₄ alkyl, wherein C₁-C₄ alkyl is
optionally substituted with C₁-C₄ alkyl, -OR⁷,
-S(O)₂R¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;
- R⁵ is independently selected at each occurrence from
15 C₁-C₆ alkyl, aryl, heterocyclyl, C₁-C₄ haloalkyl,
halo, -CN, -NO₂, -NR⁶R⁷, -COR⁷, -OR⁷, -CONR⁶R⁷,
-CON(OR⁹)R⁷, -CO₂R⁷ and -S(O)_nR¹³, wherein C₁-C₆ alkyl
is substituted with 0 to 3 substituents independently
selected at each occurrence from C₁-C₄ alkyl, -NO₂,
20 halo, -CN, -NR⁶R⁷, COR⁷, -OR⁷, -CONR⁶R⁷, CO₂R⁷ and
-S(O)_nR¹³;
- R⁶ and R⁷ are independently selected at each occurrence
from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₂-C₈
alkoxyalkyl;
- 25 wherein C₁-C₄ alkyl, may be substituted with 0 to 2
substituents independently selected at each
occurrence from -OH or C₁-C₄ alkoxy groups;
- R⁸, R⁹ and R¹⁰ are independently at each occurrence H or
C₁-C₄ alkyl;
- 30 R¹² and R¹³ are independently at each occurrence C₁-C₄
alkyl or -NR⁶R⁷;
- R¹⁴ is C₁-C₄ alkyl or -NR¹⁵R¹⁶;
- R¹⁵ and R¹⁶ are independently at each occurrence H, C₁-C₄
alkyl or C₂-C₈ alkoxyalkyl;
- 35 aryl is phenyl substituted with 0 to 3 substituents
independently selected at each occurrence from

C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵,
-CO₂R¹⁵, -NO₂ and -NR¹⁵R¹⁶; and

n is independently at each occurrence 0, 1 or 2.

5 12. A composition of matter comprising compound of
Claim 11 wherein:

Z is N;

Y is NR⁴;

10 Ar is phenyl or pyridyl, each substituted with 2 to 4 R⁵
groups;

R¹ is H, methyl, ethyl, cyclopropyl, -CF₃, or -N(CH₃)₂;

R³ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,
C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl or aryl,

15 wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or
C₃-C₆ cycloalkyl is each substituted with 0 to 3
substituents independently selected at each
occurrence from C₁-C₄ alkyl, C₃-C₆ cycloalkyl, -CF₃,
halo, -CN, -OR⁷, and aryl;

20 R⁴ is H, methyl, ethyl, i-propyl, n-propyl, n-butyl,
i-butyl, s-butyl, n-butyl, or allyl;

R⁵ is independently selected at each occurrence from
methyl, ethyl, i-propyl, n-propyl, aryl, -CF₃, halo,
-CN, -N(CH₃)₂, -C(=O)CH₃, -OCH₃, -OCH₂CH₃, -OCF₃, and
25 -S(O)₂CH₃;

R¹⁴ is C₁-C₄ alkyl or -NR¹⁵R¹⁶;

R¹⁵ and R¹⁶ are independently at each occurrence H, C₁-C₄
alkyl or C₂-C₈ alkoxyalkyl;

30 aryl is phenyl substituted with 0 to 3 substituents
independently selected at each occurrence from
C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵,
-CO₂R¹⁵, -NO₂ and -NR¹⁵R¹⁶; and

n is independently at each occurrence 0, 1 or 2.

35 13. A composition of matter comprising compound of
Claim 9 wherein:

Z is N;

Y is NR⁴ or O;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵ groups;

- 5 R¹ is H, halo, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, aryl, heterocyclyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CONR⁶R⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, or -NR⁶R⁷,
- 10 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl or C₃-C₈ cycloalkyl is each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo, C₁-C₄ haloalkyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl;
- 15 R³ is C₁-C₄ alkyl, -CN, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, -OR⁷, -COR⁷, -CO₂R⁷ or -CONR⁶R⁷, wherein C₁-C₄ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, halo, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷, -NR⁸CO₂R⁷, -NR⁶R⁷ and -CONR⁶R⁷;
- 20 R⁴ is H, C₁-C₆ alkyl or C₂-C₆ alkenyl, wherein C₁-C₆ alkyl is optionally substituted with C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, -OR⁷, -S(O)_nR¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;
- 25 R⁵ is independently selected at each occurrence from C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, heterocyclyl, -NO₂, halo, -CN, C₁-C₄ haloalkyl, -NR⁶R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷, -OR⁷, -COR⁷, -CO₂R⁷, -CONR⁶R⁷, -CON(OR⁹)R⁷ and -S(O)_nR¹³,
- 30 wherein C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl are substituted with 0 to 3 substituents independently
- 35

selected at each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN, -OR⁷, -COR⁷, -CO₂R⁷, -CONR⁶R⁷, -NR⁶R⁷, -NR⁸COR⁷, -NR⁸CO₂R⁷ and -S(O)_nR¹³;

- 5 R⁶ and R⁷ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl, heterocyclyl(C₁-C₄ alkyl)-, morpholinoethyl, morpholinopropyl and
- 10 morpholinobutyl; or NR⁶R⁷ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine; wherein C₁-C₄ alkyl, may be substituted with 0 to 2 substituents independently selected at each
- 15 occurrence from -OH or C₁-C₄ alkoxy groups; R⁸ is independently at each occurrence H or C₁-C₄ alkyl; R⁹ and R¹⁰ are independently at each occurrence selected from H, C₁-C₄ alkyl and C₃-C₆ cycloalkyl;
- 20 R¹¹ is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or C₃-C₆ cycloalkyl; R¹² is C₁-C₄ alkyl, C₁-C₄ haloalkyl or -NR⁶R⁷;
- R¹³ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR⁶R⁷, aryl, aryl(C₁-C₄ alkyl)-, heterocyclyl or
- 25 heterocyclyl(C₁-C₄ alkyl)-; R¹⁴ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₆ cycloalkyl, C₄-C₁₂ cycloalkylalkyl, -NR¹⁵R¹⁶;
- R¹⁵ and R¹⁶ are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈
- 30 alkoxyalkyl, C₃-C₆ cycloalkyl and C₄-C₁₂ cycloalkylalkyl; or -NR¹⁵R¹⁶ taken together as a whole is piperidine, pyrrolidine, piperazine, N-methyl-piperazine, morpholine or thiomorpholine;
- 35 aryl is phenyl or naphthyl, each substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵,

-S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵,
-NR⁸CONR¹⁵R¹⁶, -NR⁸CO₂R¹⁵ and -NR¹⁵R¹⁶;

heterocyclyl is pyridyl, pyrimidinyl, triazinyl, furanyl,
thienyl, imidazolyl, thiazolyl, pyrrolyl, oxazolyl,
isoxazolyl or pyrazolyl, each substituted with 0 to 3
substituents independently selected at each
occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵,
-S(O)_nR¹⁴, -CO₂R¹⁵, -NO₂, -NR⁸COR¹⁵, -NR⁸CONR¹⁵R¹⁶,
-NR⁸CO₂R¹⁵, and -NR¹⁵R¹⁶; and

n is independently at each occurrence 0, 1 or 2.

14. A composition of matter comprising compound of
Claim 13 wherein:

15 Z is N;

Y is NR⁴;

Ar is phenyl or pyridyl, each substituted with 0 to 4 R⁵
groups;

20 R¹ is H, halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,
C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, aryl,
heterocyclyl, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CONR⁶R⁷,
-CO₂R⁷ or -NR⁶R⁷,

25 wherein C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or
C₃-C₆ cycloalkyl is each substituted with 0 to 3
substituents independently selected at each
occurrence from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halo,
C₁-C₄ haloalkyl, -CN, -OR⁷, -SH, -S(O)_nR¹³, -COR⁷,
-CO₂R⁷, -OC(O)R¹³, -NR⁸COR⁷, -N(COR⁷)₂, -NR⁸CONR⁶R⁷,
-NR⁸CO₂R⁷, -NR⁶R⁷, -CONR⁶R⁷, aryl and heterocyclyl;

30 R³ is C₁-C₄ alkyl, -CN, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl,
-OR⁷, -COR⁷ or -CO₂R⁷,

35 wherein C₁-C₄ alkyl is substituted with 0 to 3
substituents independently selected at each
occurrence from C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl,
halo, -CN, -OR⁷, -S(O)_nR¹³, -COR⁷, -CO₂R⁷, -NR⁸COR⁷,
-NR⁶R⁷ and -CONR⁶R⁷;

- R^4 is H, allyl, or C₁-C₄ alkyl, wherein C₁-C₄ alkyl is optionally substituted with C₁-C₄ alkyl, -OR⁷, -S(O)₂R¹², -CO₂R⁷, -NR⁶R⁷ or -NR⁹COR¹⁰;
- R^5 is independently selected at each occurrence from C₁-C₆ alkyl, aryl, heterocyclyl, C₁-C₄ haloalkyl, halo, -CN, -NO₂, -NR⁶R⁷, -COR⁷, -OR⁷, -CONR⁶R⁷, -CON(OR⁹)R⁷, -CO₂R⁷ and -S(O)_nR¹³, wherein C₁-C₆ alkyl is substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, -NO₂, halo, -CN, -NR⁶R⁷, COR⁷, -OR⁷, -CONR⁶R⁷, CO₂R⁷ and -S(O)_nR¹³;
- R^6 and R^7 are independently selected at each occurrence from H, C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₂-C₈ alkoxyalkyl; wherein C₁-C₄ alkyl, may be substituted with 0 to 2 substituents independently selected at each occurrence from -OH or C₁-C₄ alkoxy groups;
- R^8 , R^9 and R^{10} are independently at each occurrence H or C₁-C₄ alkyl;
- R^{12} and R^{13} are independently at each occurrence C₁-C₄ alkyl or -NR⁶R⁷;
- R^{14} is C₁-C₄ alkyl or -NR¹⁵R¹⁶;
- R^{15} and R^{16} are independently at each occurrence H, C₁-C₄ alkyl or C₂-C₈ alkoxyalkyl;
- aryl is phenyl substituted with 0 to 3 substituents independently selected at each occurrence from C₁-C₄ alkyl, halo, -CN, -OR¹⁵, -S(O)_nR¹⁴, -COR¹⁵, -CO₂R¹⁵, -NO₂ and -NR¹⁵R¹⁶; and
- n is independently at each occurrence 0, 1 or 2.

15. A method for treating affective disorders, anxiety, depression, post-traumatic stress disorders, supranuclear palsy, seizure disorders, stroke, irritable bowel syndrome, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other eating disorders, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorders, or fertility problems in

a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of a compound of formula (I) as defined in any one of Claims 1-14.

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16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I) as defined in any one of Claims 1-14.

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INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/US 97/16252

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D241/20 A61K31/495 C07D401/12 C07D405/12 C07D253/07
C07D241/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 95 33750 A (PFIZER) 14 December 1995 cited in the application see the whole document ---	1-16
Y	WO 94 13676 A (PFIZER) 23 June 1994 cited in the application see the whole document ---	1-16
A	EP 0 242 957 A (TOYO JOZO KABUSHIKI KAISHA) 28 October 1987 see page 43-49; claim 1 -----	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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S document member of the same patent family

Date of the actual completion of the international search

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